AMBULATORY CARE
SELF-ASSESSMENT PROGRAM

ACSAP

2017 • BOOK 1

ONCOLOGIC/ HEMATOLOGIC CARE

Series Editors
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AMERICAN COLLEGE OF CLINICAL PHARMACY

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A Message From the Editors

As the Ambulatory Care Self-Assessment Program (ACSAP) begins its second 3-year series, we would like to take a moment to assess how the inaugural 2013–2015 series fulfilled its mission of providing evidence-based information to improve the practice skills of clinicians and enhance patient care in this setting.

The first ACSAP series released six books with a total of 19 learning modules comprising 63 chapters. The content of each book was designed by a volunteer faculty panel chair (guest editor) using topics drawn from the content outline developed by the Board of Pharmacy Specialties for the Ambulatory Care Pharmacy Specialty Certification Examination. Each faculty panel chair then recruited author teams and content expert reviewers for each chapter. To ensure the appropriateness and relevance of content to the audience, each chapter was also reviewed by one or more generalist BCACP reviewers. This year-long editorial process also required the efforts of dozens of other volunteers to pilot test the chapter material and self-assessment questions and to review ACSAP materials to ensure that they were free from commercial bias. We learned that it takes an army of contributors committed to this specialty and the board certification process to produce a new recertification component for the BCACP.

The 2013–2015 ACSAP chapters covered the domains of direct patient care; practice management; public health, retrieval, generation, interpretation, and dissemination of knowledge; and patient advocacy. The six books provided a total available 121 BCACP recertification credits. Readers submitted 1333 posttests for recertification in 2013. The next year, 2285 tests were submitted (a 71% increase). In 2015, readers submitted 3077 posttests for recertification credit (a 35% increase over 2014).

The users of ACSAP also provided us with a great deal of guidance for this new edition. Features they found to be useful are preserved, including the Patient Care Scenarios and Practice Points boxes; hyperlinks to data compilers, assessment tools, and patient resources; color photographs and illustrations; patient care algorithms; and informational videos. New features include a chapter redesign to make this information easier to read in the online format and the bundling of the online and e-media formats so that each book can be viewed not only as a PDF but also on a smartphone, tablet, or e-reader.

As series editors, we rededicate ourselves to the goal of providing a recertification offering that, through its depth of information, ease of access, and emphasis on clinical application, will have an immediate and positive impact on the care of patients in the ambulatory care setting. We also express our gratitude to the many volunteer contributors who lent their energy and expertise to this important new series.

Betty J. Dong and David P. Elliott, series editors

Oncologic Care I

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Cancer Screening and Prevention

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LEARNING OBJECTIVES

1. Evaluate the risks and benefits of cancer screening and prevention.
2. Assess the differences in cancer prevention therapies for patients with normal- and high-risk breast cancer.
3. Construct a cancer prevention plan for a patient at risk of breast, colorectal, human papillomavirus–related, or prostate cancer.
4. Distinguish between cancer screening guideline recommendations for breast, cervical, colorectal, lung, and prostate cancers.
5. Design an appropriate cancer-screening plan for an individual patient according to cancer-screening guidelines and individual risk factors.

ABBREVIATIONS IN THIS CHAPTER

ACOG	American Congress of Obstetricians and Gynecologists
ACP	American College of Physicians
ACS	American Cancer Society
AUA	American Urological Society
CBE	Clinical breast examination
CRC	Colorectal cancer
DRE	Digital rectal examination
FIT	Fecal immunochemistry test
gFOBT	Guaiac-based fecal occult blood test
HPV	Human papillomavirus
LCIS	Lobular carcinoma in situ
NCCN	National Comprehensive Cancer Network
PSA	Prostate-specific antigen
SERM	Selective estrogen receptor modifier
USPSTF	U.S. Preventive Services Task Force

Table of other common abbreviations.

INTRODUCTION

In 2016, an estimated 1,685,210 new cancers will be diagnosed, and about 595,690 Americans will die of cancer (ACS 2016a). Many cancers can be prevented. Moreover, patients can be screened for cancer to detect and remove precancerous lesions and/or detect cancer early, which reduces morbidity and mortality. Cancer prevention or risk reduction is thought to reduce cancer mortality. This can be accomplished by (1) avoiding carcinogens or altering the metabolism of the carcinogen (e.g., use of dietary or pharmaceutical chemoprevention); (2) modifying lifestyle or dietary practices that alter cancer-causing factors or genetic predispositions; (3) using chemoprevention; or (4) using early detection procedures to remove precancerous lesions. Prevention can be categorized as primary, secondary, and tertiary. Primary prevention includes interventions to prevent the development of cancer (e.g., avoiding carcinogens, modifying lifestyles, using chemoprevention), whereas secondary prevention includes interventions leading to the discovery and control of cancer or precancerous lesions (e.g., screening and early detection). Tertiary prevention is the use of treatment once cancer is diagnosed to reduce the complications and progression or recurrence of cancer.

Several carcinogens have causally been associated with the development of cancer, including cigarette/tobacco use, infections, immunosuppression, and radiation therapy (Box 1-1). Other risk factors that have been implicated in cancer development include diet, obesity, and diabetes. For example, a diet high in fruit and vegetable consumption has been associated with protection against esophageal, mouth, stomach, and possibly lung cancers, whereas a diet high in red and processed meat is associated with an increased risk of developing colorectal and stomach cancer. Because data are limited and often based on observational studies, no specific dietary recommendations are provided; rather, individuals should have a well-balanced diet, much like what one would do to maintain cardiovascular health.

In cancer screening, cancer is found using a procedure or blood test at an early stage, often before symptoms appear. Data vary on the number of premature deaths (3%–35%) that are avoided using screening (NCI 2016). In addition to avoiding premature deaths, screening may reduce cancer morbidity because treatments for early-stage cancers are often better tolerated than those for more advanced-stage cancers and, in some cases, allow for removal of precancerous lesions, such as with colonoscopy.

Box 1-1. Carcinogens Associated with Cancer Development

Cigarette/Tobacco Use

- Acute myelogenous leukemia
- Bladder
- Cervix
- Esophagus
- Kidney
- Lung
- Oral cavity
- Pancreas
- Stomach

Infections

- Epstein-Barr virus
  - Burkitt lymphoma
- *Helicobacter pylori*
  - Gastric
- Human papillomavirus
  - Anal
  - Cervical
  - Oropharyngeal
  - Penile
  - Vaginal
  - Vulvar
- Hepatitis B and C
  - Liver

Immunosuppression

- Non-Hodgkin lymphoma
- Kidney
- Liver
- Lung

Radiation

- Ionizing radiation
  - Breast
  - Hematologic malignancies (i.e., leukemia, lymphoma)
  - Lung
  - Thyroid
- UV radiation
  - Melanoma
  - Nonmelanoma skin cancers

Information from: Engels EA, Pfeiffer RM, Fraumeni JF, et al. Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891-901; and National Cancer Institute. Cancer Prevention.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the most common cancers in the United States
- Basic understanding of cancer prevention and screening concepts
- Drug knowledge of agents used for chemoprevention
- Knowledge of general statistical concepts used to evaluate a clinical test

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Cancer Society. Guidelines for Early Detection of Cancer.
- Lalkhen AG. Clinical tests: sensitivity and specificity. Cont Ed Anaesth Crit Care Pain 2008;8:221-3.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
- National Cancer Institute. Cancer Prevention.
- National Cancer Institute. Cancer Screening.

Cancer prevention and screening are not without risks, however, and the potential harms must be considered against the potential benefits (Kramer 2004). The risks of cancer prevention primarily reside in the potential adverse effects or complications of chemoprevention or early detection removal procedures. Cancer prevention strategies may also provide a false sense of protection from cancer because no one preventable strategy is fully protective. Although cancer screening is typically noninvasive or minimally invasive, complications may occur (e.g., perforation during colonoscopy). In addition, false test results may lead to anxiety or unnecessary further testing, which may carry its own risks (false

positive) or falsely reassure an individual who may ignore subsequent signs and symptoms of cancer, possibly delaying diagnosis and treatment (false negative). Overdiagnosis or lead-time bias is also a concern. For example, some prostate cancers are indolent and not clinically important. Diagnosing a slow-growing lesion may then lead to overtreatment and possible morbidity and earlier mortality because of the treatment (overdiagnosis) or have no change at all on mortality (lead-time bias). Lead-time bias can also result in additional morbidity from unneeded treatments and the emotional impact on the diagnosis and treatment.

CANCER PREVENTION

Although prevention of cancer would be ideal, effective prevention strategies are currently available for only some cancers. Cancers for which evidence supports cancer prevention strategies in patients include breast cancer, colorectal cancer (CRC), human papillomavirus (HPV)-related cancers (anal, cervical, penile, vaginal, vulvar cancers), ovarian cancer, and prostate cancer. This chapter focuses on primary prevention of cancer, rather than secondary or tertiary prevention of cancer.

Breast Cancer

Most breast cancers are not related to risk factors other than increasing age and female sex. However, some women are at increased risk because of familial/genetic factors (e.g., breast cancer gene 1 or 2 [*BRCA1* or *BRCA2*), age (e.g., increasing age), ethnicity/race (e.g., Ashkenazi Jewish descent), lifestyle factors (e.g., increased BMI, alcohol consumption), reproductive history (e.g., younger age at menarche, low or nulliparity), and/or disease risks (e.g., history of lobular carcinoma in situ [LCIS] or radiation to thoracic area at younger than 30) (NCCN 2016a). In patients with any of these risk factors who are 35 and older, the Gail model is used to determine the individual's 5-year breast cancer risk (Gail 2001; Spiegelman 2001; Gail 1989). The National Cancer Institute has a freely available risk assessment tool using the Gail model. In women with a calculated 5-year relative risk of 1.7% or higher and a life expectancy of 10 years or more or in those with a known genetic predisposition, such as *BRCA1* and/or *BRCA2* mutation positive, cancer prevention options should be offered, together with a risk-benefit discussion. For these women at higher risk, specific cancer prevention, also sometimes known as risk reduction strategies, can be used. All women could benefit from lifestyle modifications, such as minimal alcohol consumption (less than 1 alcoholic drink per day equivalent to 1 oz of liquor, 6 oz of wine, or 8 oz of beer), a healthy well-rounded diet, and regular exercise to minimize obesity and weight gain. The following discussion of breast cancer prevention focuses on primary prevention only. Although women with a diagnosis of breast cancer may be at an increased risk of developing a contralateral breast cancer, the recommendations that follow do not apply. Instead, women with a diagnosis of breast cancer may typically receive breast cancer treatment that is aimed at reducing the recurrence of cancer anywhere within the body, including in the contralateral breast. For current, specific recommendations on such therapy, the National Comprehensive Cancer Network (NCCN) is a good resource.

Patients with the BRCA1- *or* BRCA2 *Mutation*

Women with the *BRCA1* or *BRCA2* mutation have an estimated lifetime risk of developing breast cancer of 56%–84% (Antoniou 2006; Ford 1998; Struewing 1997). In addition, these women are at a high risk of developing ovarian cancer (36%–46% in *BRCA1* and 10%–27% in *BRCA2*) (Antoniou 2003; King 2003; Satagopan 2002; Prevalence 2000; Ford 1998). With this high risk of developing breast cancer, the use of bilateral mastectomy has been investigated as a cancer prevention strategy. Retrospective analyses have indicated that bilateral mastectomy in *BRCA1* and/or *BRCA2* mutation carriers reduces the risk of breast cancer by at least 90% (Hartmann 2001; Hartmann 1999). A recent meta-analysis of four prospective studies (about 2600 patients) has confirmed a significant risk reduction of breast cancer after bilateral mastectomy (HR 0.07; 95% CI, 0.01–0.44; p=0.004) (De Felice 2015). Similarly, prophylactic bilateral salpingo-oophorectomy is effective in reducing the risk of breast cancer by about 50%, as well as ovarian/fallopian tube cancer by 80% (Rebbeck 2009; Eisen 2005; Rebbeck 2002; Rebbeck 1999). Given these data, the NCCN recommends that bilateral total mastectomy (with or without reconstruction), alone or in combination with bilateral salpingo-oophorectomy, in women with the *BRCA1* or *BRCA2* mutation who desire risk reduction after counseling, as an appropriate cancer prevention option (NCCN 2016a). Risk-reduction agents are not routinely recommended at this time because either no (raloxifene; aromastase inhibitors) or limited (tamoxifen) data in this population exist. (See the section on ovarian cancer for prevention strategies.)

Women 35 and Older

In women 35 and older who have a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the Gail model, chemoprevention with selective estrogen receptor modifiers (SERMs) or aromatase inhibitors may be beneficial as a prevention strategy.

Selective Estrogen Receptor Modifiers

Tamoxifen and raloxifene significantly reduce the risk of breast cancer. In the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (P-1 trial), women 60 and older, pre- or postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the GAIL risk model, and women with a history of LCIS were randomized to tamoxifen 20 mg by mouth daily for 5 years or placebo (Fisher 1998). The short-term risk of developing breast cancer in women 35 and older decreased by 49% at 5 years and 43% at 7 years.

The number needed to treat was 47. In this study, after 7 years of follow-up, a reduction in bone fractures occurred (RR 0.68; 95% CI, 0.51–0.92), but tamoxifen was associated with an increase in pulmonary embolism (RR 2.15; 95% CI, 1.08–4.51), and more cases of endometrial cancer, hot flashes, and cataracts occurred. A slightly higher rate of pulmonary embolism occurred in women older than 50 (RR 2.16; 95% CI, 1.02–4.89) (Fisher 2005). Other chemoprevention studies of tamoxifen in women at higher risk of developing breast cancer have had similar efficacy results (NCCN 2016a).

Raloxifene is a second-generation SERM that has less endometrial stimulation than tamoxifen but similar antiestrogenic activity. In the National Surgical Adjuvant Breast and Bowel Project STAR trial (P-2 trial), postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer as determined by the GAIL risk model or a history of LCIS were randomized to tamoxifen 20 mg by mouth daily or raloxifene 60 mg by mouth daily (Vogel 2006). After 4 years of therapy, the relative risk of developing breast cancer was similar between the two agents (RR 1.02; 95% CI, 0.82–1.28). However, by 8 years, tamoxifen was more likely to decrease risk (RR 1.24; 95% CI, 1.05–1.47). The raloxifene group had a lower incidence of thromboembolic events, cataract development, and endometrial cancer.

Despite raloxifene's potentially lower incidence of adverse effects, tamoxifen is the preferred chemopreventive agent, especially in younger women, because of its superior long-term efficacy. Tamoxifen can be used in both pre- and postmenopausal women, whereas raloxifene has proven efficacy only in postmenopausal women. Raloxifene, however, may be preferred in postmenopausal women older than 50 with a uterus because it does not increase the risk of endometrial cancer or cataract development (NCCN 2016a). All women should be counseled on the signs/symptoms of thromboembolism. Contraindications for tamoxifen or raloxifene include history of thrombotic conditions (e.g., thromboembolism, thrombotic stroke, transient ischemic attack) or current pregnancy or potential for pregnancy without adequate contraception. Five years of chemoprevention is the current recommendation for these agents, although women may benefit from longer durations.

Aromatase Inhibitors

Aromatase inhibitors (anastrozole, letrozole, exemestane) are effective in the treatment of breast cancer. Furthermore, these agents do not have estrogenic activity, compared with SERMs. Because early treatment trials found that these agents decreased the risk of contralateral breast cancer, they were then evaluated for breast cancer reduction. The Mammary Prevention 3 trial randomized in double-blind fashion women 60 and older, pre- or postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer, or women with a history of atypical ductal or lobular hyperplasia or LCIS to receive exemestane 25 mg or placebo by mouth daily. Those treated with exemestane had a reduction in breast cancer incidence compared with those receiving placebo (HR 0.35; 95% CI, 0.18–0.70) (Goss 2011). The International Breast Cancer Intervention Study II evaluated anastrozole 1 mg by mouth daily versus placebo in a similar high-risk group of women. These results also showed that anastrozole resulted in reduced breast cancer incidence (HR 0.47; 95% CI, 0.23–0.68) (Cuzick 2014). The most common adverse effects reported in these trials were arthritis, arthralgia, and hot flashes. In addition, patients were more likely to develop bone loss and ultimately fracture, given the antiestrogenic activity in bone. Because of these trials, the NCCN breast cancer reduction guidelines recommend either exemestane 25 mg by mouth daily for 5 years or anastrozole 1 mg by mouth daily for 5 years for chemoprevention in postmenopausal women 35 and older with a cumulative 5-year risk of 1.7% or greater of developing breast cancer or a history of LCIS. Neither of these agents is currently FDA approved for this indication. An aromatase inhibitor for chemoprevention may be appropriate for postmenopausal women with normal or stable bone density or for those with comorbid conditions that preclude the use of a SERM (see Figure 1-1).

Colorectal Cancer

Many studies have evaluated agents for the chemoprevention of CRC in high-risk individuals and those within the general population. Current guidelines, however, recommend the use of aspirin only for chemoprevention.

Aspirin, NSAIDs, and Cyclooxygenase-2 Inhibitors

According to the results of observational studies, taking at least two doses per week of aspirin or an NSAID is associated with a reduced risk of CRC. In an average-risk individual, regular aspirin use (80–320 mg/day) is associated with a 20%–40% reduction in the risk of colorectal adenoma and CRC (Teixeira 2014). In patients with a history of adenomas or diagnosis of CRC, regular daily aspirin use reduces colorectal adenoma recurrence and CRC incidence and mortality. Benefit has also occurred with NSAID and cyclooxygenase 2 (COX-2) inhibitor use, primarily with sulindac and celecoxib. For example, a 30%–45% reduction in the risk of CRC occurred with celecoxib (200–400 mg/day) use over a 10- to 15-year period (Teixeira 2014). In patients with a history of adenomas, combining sulindac (150 mg/day) with ornithine decarboxylase inhibitor difluoromethylornithine (500 mg/day) resulted in a 70% reduction in adenomas, but this was limited by ototoxicity and cardiotoxicity. The protective effects of these agents appear to be related to their inhibition of COX-2 and free radical formation.

However, the optimal dosing and duration of aspirin, NSAIDs, and COX-2 inhibitors remain to be determined, and potential cardiovascular events, gastric ulceration, and bleeding with these agents are possible. Although NSAIDs may be appropriate for selected individuals at a high risk of CRC but

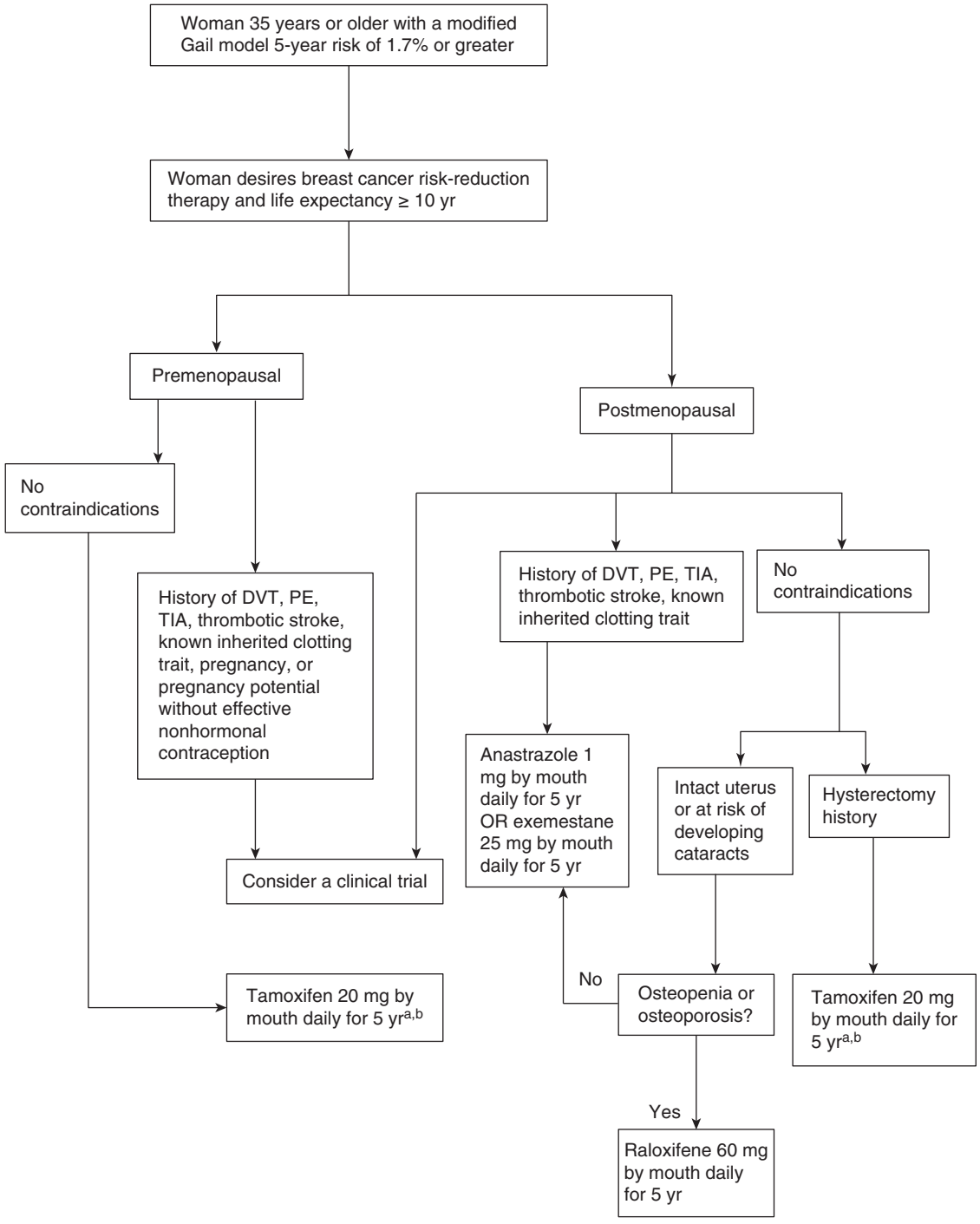

Figure 1-1. Algorithm for the selection of breast cancer risk-reduction treatments.

[a]Review concurrent medications for CYP2D6 inhibitors, which may inhibit tamoxifen metabolism. Consider alternative medications.

[b]May be an option for patients who are carriers of the *BRCA1* or *BRCA2* mutation or who have had prior thoracic irradiation.

[c]Postmenopausal women with no contraindications may receive therapy with tamoxifen, raloxifene, or an aromatase inhibitor (anastrazole or exemestane). Preference for therapy may depend on medical history, as indicated by algorithm, but these are not contraindications.

DVT = deep venous thromboembolism; PE = pulmonary embolism; TIA = transient ischemic attack.

Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Risk Reduction Screening, version 1. 2016.

low risk of cardiovascular disorders, the U.S. Preventive Services Task Force (USPSTF) has concluded that the potential harms associated with NSAID use (other than aspirin) outweigh the benefits for prevention of CRC in the general population (USPSTF 2016). New USPSTF guidelines recommend daily low-dose aspirin (75–100 mg by mouth daily or 100–325 mg by mouth every other day) for at least 10 years in patients age 50–59 who have a life expectancy of at least 10 years and are not at risk of bleeding for primary prevention of cardiovascular disease and CRC. Adults age 60–69 may also receive low-dose daily aspirin for at least 10 years if the benefits outweigh the risks. The greatest benefit of low-dose aspirin in adults age 50–59 is when the 10-year cardiovascular disease risk is 10% or greater. Older adults may also benefit, although the net benefit is smaller because of the increased risk of GI bleeding and the decrease in CRC prevention. The 10-year cardiovascular risk can be calculated using the online risk calculator.

No other guidelines recommend aspirin use for primary prevention of CRC in average-risk adults. Both the American Gastroenterological Association and the NCCN limit their recommendation to patients at increased risk of CRC (Chubak 2015).

Hormone Replacement Therapy

Exogenous postmenopausal oral hormone replacement therapy (estrogen, progesterone, or the combination) is associated with a significant reduction in CRC risk, which persists for about 10 years after therapy is discontinued (Teixeira 2014). However, because postmenopausal hormone replacement therapy increases breast cancer risk and harmful cardiovascular effects, its use is not recommended to prevent CRC.

Polyp Removal

A history of high-risk adenomatous polyps, particularly multiple adenomas or those 10 mm or greater, is associated with an increased risk of CRC (NCCN 2015a). Colonoscopic polypectomy done during a screening colonoscopy is considered the standard of care for all individuals to prevent the progression of premalignant adenomatous polyps to colon cancer lesions. Although no randomized trials show that colonoscopy decreases CRC mortality, results of observational studies not only show a 56%–77% decrease in the incidence in CRC with colonoscopy and polyp removal but also about a 50% reduction in CRC mortality (NCCN 2015a). Therefore, one of the best prevention strategies for CRC is to remove any polyps that are found during colonoscopy. As discussed in the colorectal cancer section that follows, colonoscopy is the gold standard screening measure because it allows for immediate identification and removal of polyps.

HPV-Related Cancers

Human papillomavirus is responsible for almost all (99.7%) cervical cancers (Bailey 2016). Human papillomavirus–related cancers affect both men and women, with HPV causing 60% of oropharyngeal cancers, 63% of penile cancers, 69% of vulvar cancers, 75% of vaginal cancers, and 91% of anal cancers. The most common HPV genotype responsible for these cancers is 16, but several other HPV genotypes (6, 11, 18, 31, 33, 45, 52, and 58) have been associated with cancer as well. Human papillomavirus–related cancers appear to occur disproportionately in health-disparate groups (lower income, lower educational attainment). This may be because of low screening and treatment rates and higher behavioral risk factors, such as early age of first sexual activity.

HPV Vaccines

Three HPV vaccines on the market are effective in preventing many cancers related to HPV (Bailey 2016), including most anal, cervical, penile, vaginal, and vulvar cancers caused by HPV. Although it is known that HPV causes some forms of oropharyngeal cancer, the effectiveness of the HPV vaccine in this setting is unknown. Table 1-1 summarizes the properties, effectiveness, and recommendations for using HPV for cancer prevention. All three of these vaccines are administered as a 3-injection series: initially and 1–2 months and 6 months after initial injection. Ongoing studies are evaluating the possibility of a 1- or 2-injection series in hopes of gaining better compliance with guidelines without compromising efficacy. The current CDC Advisory Committee on Immunization Practices guidelines recommend that girls and boys age 11–12 years (but as early as 9 years) receive HPV vaccination (CDC 2016). Men age 22–26 if they have sex with men or females and men age 22–26 who are immunocompromised should also receive the 3-injection vaccine series. Currently, compliance with CDC Advisory Committee on Immunization Practices guideline recommendations is about 30% (Hopkins 2013). Barriers to vaccination include patient factors (e.g., lack of education and/or discomfort about sexual behavior discussions) and system factors (e.g., reimbursement, reminders about timing of vaccines).

Ovarian Cancer

The association between oral contraceptive use and decreased ovarian cancer risk has been studied in many trials and epidemiologic studies. A potential mechanism for the benefit is that taking oral contraceptives can lead to anovulation. The lack of ovulation leads to less repeated trauma to the ovarian epithelium, which causes a decreased cancer risk. Two large studies support the use of oral contraceptives in decreasing the risk of ovarian cancer (Faber 2013; Vessey 2013). The final results of a cohort study of over 17,000 women in England and Scotland showed that using oral contraceptives decreased the relative risk of developing ovarian cancer by 50% (95% CI, 0.4–0.7) (Vessey 2013). This study included women mainly taking oral contraceptives containing 50 mcg of estrogen or more, which is higher than today's standard oral contraceptives, but showed that the decreased

Table 1-1. Currently Available HPV Vaccines[a]

HPV Vaccine Type	Bivalent	Quadrivalent	9-Valent
Trade name (Manufacturer)	Cervarix (GlaxoSmithKline)	Gardasil (Merck)	Gardasil 9 (Merck)
HPV genotypes	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Effectiveness	Protects against anal (78% men), anal or cervical (96% women), penile (100%), vaginal (100%), vulvar (100%), and genital warts (99% females, 91% males) caused by these genotypes 5-year protection, ongoing study evaluating full effect		Protects against anal (75%, men), anal or cervical (96% women), penile (100%), vaginal (100%), vulvar (100%), and genital warts (99% females, 89% males) caused by these genotypes
CDC ACIP guidelines	Girls age 11–12 years (but as young as 9 years[b]) receive any of these HPV vaccines Boys age 11–12 years (but as young as 9 years[b]) receive only 4- or 9-valent HPV vaccine Men age 22–26 if they have sex with men or women or males who are immunocompromised should receive the 3-injection series		

[a]All HPV vaccines administered as 3-injection series: initial and 1–2 months, and 6 months after initial injection. A catch-up schedule is provided in the guidelines.

[b]May be initiated in children as young as 9 years, particularly in those with history of sexual abuse or assault.

ACIP = Advisory Committee on Immunization Practices; HPV = human papillomavirus.

Information from: CDC. Immunization Schedules [homepage on the Internet].

risk of ovarian cancer continued the longer the patients were on active therapy. In another population-based case-control study, the decrease in risk occurred regardless of the amount of estrogen and progesterone and did not depend on whether the contraceptives were combined hormone therapy or progestin only (Faber 2013). The results of this study show that use of combined oral contraceptives is associated with a statistically significantly decreased risk of ovarian cancer (OR 0.68; 95% CI, 0.53–0.88) and that mixed use of combined and progestin-only pills decreases the risk (OR 0.50; 95% CI, 0.28–0.87). Although these studies report a decreased risk, no current guidelines recommend that all childbearing women use oral contraceptives. Risks (thromboembolism, breast cancer risk with duration > 5 years, continued ovarian cancer screening in women at high risk [e.g., *BRAC1* or *2* mutation]) and benefits should still be considered for each individual woman.

Patients with the *BRCA1* and/or *BRCA2* mutation are also at a high risk of developing ovarian cancer. As discussed in the Cancer Prevention: Breast Cancer section, bilateral salpingo-oophorectomy reduces the risk of ovarian and fallopian tube cancer in women with the *BRCA1* and/or *BRCA2* mutation by about 80% (NCCN 2017). Although chemoprevention with SERMs may help reduce invasive breast cancer in these women, it is not protective against ovarian cancer. Ovarian cancer screening with ultrasonography and CA-125 concentrations is not considered routinely recommended but is advocated by some.

Prostate Cancer

Most prostate cancers occur after age 40, and lifelong exposure to testosterone is thought to be the likely causative factor. Therefore, the use of agents to reduce testosterone concentrations could be effective in preventing prostate cancer.

5-α-Reductase Inhibitors

The enzyme 5-α-reductase converts testosterone to its more active form, dihydrotestosterone, which is responsible for prostate epithelial cell proliferation (Thompson 2003). In fact, continuous use of the 5-α-reductase inhibitors finasteride and dutasteride lowers prostate-specific antigen (PSA) concentrations by as much as 50% after 6 months (NCCN 2016b). Two clinical trials have evaluated these drugs for prostate cancer prevention. The Prostate Cancer Prevention Trial (PCPT) compared finasteride 5 mg orally daily with placebo for 7 years in 18,882 men 55 and older with a normal digital rectal examination (DRE) and a PSA concentration less than 3 ng/mL (Thompson 2003). The trial results showed that finasteride reduced the incidence of prostate cancer by 30% (10.5% vs. 14.9%; RR 0.70; 95% CI, 0.65–0.76, p<0.001). The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial evaluated dutasteride 0.5 mg by mouth daily versus placebo for 4 years in 6729 men age 50–75 with a normal DRE and a PSA concentration of 2.5–10 ng/mL and one negative prostate cancer biopsy within

6 months of enrollment. Similar to the PCPT study, dutasteride significantly reduced the incidence of prostate cancer with a relative risk reduction of 22.8% (95% CI, 15.2–20.8; p<0.001) (Andriole 2010). However, in both studies, the number of men who died of prostate cancer was similar (Thompson 2013; Andriole 2010; Thompson 2003). Furthermore, men receiving 5-α-reductase inhibitor chemoprevention in these trials who later developed prostate cancer tended to have higher-grade tumors (i.e., Gleason score 7–10), and sexual dysfunction adverse effects were commonly reported. Thus, according to these study results, the FDA Oncologic Drugs Advisory Committee did not recommend either agent for chemoprevention, and these agents are not routinely used for prostate cancer prevention. Of note, a long-term follow-up (18 years) analysis of the PCPT study results showed that although more men did develop high-grade tumors, no increase in cancer mortality occurred in these men as might be expected. Thus, the incidence of high-grade tumors after finasteride therapy may not be from promotion of aggressive tumor development but from an artifact of finasteride therapy (Thompson 2013). Several ongoing trials are evaluating other chemoprevention agents that are focused on dietary supplements (e.g., lycopene).

CANCER SCREENING

Several organizations provide guideline recommendations for cancer screening. Recommendations vary on which cancers people should have screening tests for, which screening tests should be used to screen for a particular cancer, and when and how often those screening tests should be done. Recommendations for routine cancer screening are available for breast, cervical, colorectal, lung, and prostate cancers. In addition, guidance on endometrial and skin cancers will be discussed. Three organizations provide screening guidelines for each of these cancers: the American Cancer Society (ACS), NCCN, and USPSTF. In addition, professional organizations specific to the disease state (e.g., American Congress of Obstetricians and Gynecologists [ACOG] for breast cancer screening) may provide guidelines. Often, guidelines from various organizations have similar recommendations for the types of screening tests to use but different recommendations for the frequency of screening, when to start screening, and when to end screening. The NCCN screening guidelines are updated at least annually; the other guidelines are updated less often.

Individuals known to be at a high risk of cancer, such as those with a personal history of cancer or a strong family history of cancer (in two or more first-degree relatives), may require a different type, frequency, and initial timing of screening. The subsequent sections will discuss screening recommendations for normal- and high-risk patients.

Breast Cancer

Types of Screening Methods

The type of screening used for breast cancer depends on the patient's risk factors and may include breast cancer awareness, clinical breast examination (CBE), risk assessment, mammography, and, in some cases, breast MRI. Of importance, a diagnostic breast evaluation (one that evaluates an existing problem) differs from a breast screening. For example, a breast ultrasound may be used in a diagnostic workup of women who may have a lump and/or positive findings on other screening tests, but this is not part of routine screening.

A CBE includes an inspection of the breast by a health care provider in both the upright and supine positions, to detect any subtle shape or contour changes in the breast (NCCN 2015b). In addition, women should become familiar with their own breasts and promptly report any changes to their health care provider. Breast self-examination may be useful for patients to do to maintain consistent breast awareness. Risk assessment categorizing the patient into normal and high risk is important because screening recommendations differ for these two groups. High-risk patients include those with an increased lifetime risk according to models or a genetic predisposition to cancer. More details are provided in screening guidelines for high-risk patients (in the Screening Guidelines section that follows). Mammography screening involves two radiographic images of each breast: one taken from the top of the breast and one from the side of the breast. Mammography has a 75% sensitivity rate overall, but it decreases in women with dense breasts (50%) and those with a known *BRCA1* and/or *BRCA2* mutation (33%) (Berg 2008; Kuhl 2005; Carney 2003). Breast MRI screening uses a powerful magnetic field, radiofrequency pulses, and a computer to create detailed pictures of the breasts. Although the sensitivity is much higher with breast MRI (94%–100%), the specificity is lower (37%–97%), making it much more likely to cause false-positive results (Orel 2000; Orel 1994).

Screening Guidelines for Normal-Risk Patients

Each of the guidelines recommends regular breast self-examination, and the ACOG and NCCN recommend a routine CBE every 1–3 years at age 25–40 and yearly after age 40 (ACOG 2016; Sui 2016; NCCN Breast Cancer Screening 2015; Oeffinger 2015). The NCCN recently changed its CBE to include not only a CBE but also ongoing risk assessment and risk reduction counseling, if appropriate, and redefined it as a clinical encounter. Breast MRI is not recommended for normal-risk patients (ACOG 2016; NCCN Breast Cancer Screening 2015). Although all of the guidelines recommend mammography for breast cancer screening, controversy exists on its benefit, particularly in younger women. Some data suggest that mammography leads to the overdiagnosis of breast cancer, only modestly reducing the risk of breast

Table 1-2. Mammography Breast Cancer-Screening Guidelines for Normal-Risk Patients

Guideline (Year Updated)	When to Begin Screening	When to Stop Screening	Testing Frequency
American Cancer Society (2015)	Age 45[a]	Life expectancy < 10 years	Yearly until age 54, then every 2 years
American Congress of Obstetricians and Gynecologists (2011; reaffirmed 2014)	Age 40	Reevaluate life expectancy at age 75	Yearly
National Comprehensive Cancer Network (2016)	Age 40	If treatment would not occur	Yearly[b]
U.S. Preventive Services Task Force (2016)	Age 50[a]	Age 75	Every 2 years

[a]May begin at age 40.

[b]Digital tomosynthesis may be used instead of traditional mammography.

Information from: Oeffinger KC. Breast cancer screening for women at average risk. 2015 guideline update from the American Cancer Society. JAMA 2015;314:15:1599-614; American Congress of Obstetricians and Gynecologists Practice Bulletin 2011; 122:1-11; National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, version 1, 2015; Siu AL; U.S. Preventive Services Task Force. Screening for breast cancer. U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016;164:279-96.

cancer mortality (Siu 2010). Therefore, the recommendations differ regarding the timing to begin breast cancer screening and the frequency of screening tests. Over the past 15 years, the timing of breast cancer screening has changed from beginning annual screening at age 40 to starting screening at age 40–50 annually to every other year (because relative benefits of annual screening as a woman ages after menopause decreases), depending on the guideline. Breast cancer screening should stop when the patient has a life expectancy of less than 10 years or age 75. In addition, the NCCN now recommends consideration of tomosynthesis (i.e., three-dimensional radiography) as an alternative to mammography. Table 1-2 provides the most current recommendations for breast cancer screening in normal-risk patients.

Screening Guidelines for High-Risk Patients

Both the ACS and the NCCN offer guideline recommendations for patients at a high risk of developing breast cancer (ACS 2016b; NCCN Breast Cancer Screening 2015). The ACS identifies high-risk patients as women with a breast cancer lifetime risk of 20%–25% and one of the following: (1) *BRCA1* or *BRCA2* gene mutation or first-degree relative with gene mutation but patient has not been tested yet; (2) therapeutic thoracic radiation therapy at age 10–30 years; or (3) Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndrome in themselves or a first-degree relative. These high-risk patients should receive annual breast MRI and mammography screening (ACS 2016b). The NCCN recommends a mammography, CBE, and consideration of breast MRI and prevention strategies for patients at high risk (NCCN 2015b). Those at high risk within this guideline include (1) women 35 and older with a 5-year risk of invasive breast cancer of 1.7% or greater by the Gail model; (2) women with a lifetime risk of breast cancer of greater than 20% according to family history models; (3) women who have previously received therapeutic thoracic radiation therapy; (4) women with LCIS and atypical ductal or lobular carcinoma; and (5) women with a family history suggestive of genetic predisposition. Specific NCCN screening recommendations, frequency, and time to initiate screening for these patients are listed in Table 1-3.

Cervical Cancer

Before cervical cancer screening began, cervical cancer was one of the most common causes of death in women. The reduction in mortality through cervical cancer screening has occurred by detecting precancerous lesions as well as invasive cancer at early stages, thereby increasing the overall survival rate of cervical cancer to about 92% (Saslow 2012).

Types of Screening Methods

Cervical cancer screening is recommended for women from age 21 to about age 65 to reduce the morbidity and mortality from cervical cancer. Two screening methods are used: cervical cytology and HPV testing. Two methods are available for preparing a specimen for cervical cytology: the conventional Papanicolaou (Pap) smear and liquid-based cytology. Both methods use cells obtained from the external surface of the cervix and the cervical canal using a spatula and/or brush. The Pap smear is a collection of cells on a microscope slide that is examined by a pathologist under

Table 1-3. Breast Cancer-Screening Guidelines for High-Risk Patients[a]

High-Risk Feature	Screening Test	When to Begin Screening	Testing Frequency
BRCA1 or *BRCA2* mutation	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 25	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 25–29	Yearly
	Mammography and breast MRI with contrast	Age 30–75[c]	Yearly
Li-Fraumeni syndrome	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 20–25	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 25–29	Yearly
	Mammography and breast MRI with contrast	Age 30–75[c]	Yearly
Cowden syndrome/PHTS	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age 25 or 5–10 years before earliest known breast cancer in family	Every 6–12 months
	Breast MRI with contrast (mammography if MRI unavailable)	Age 30–35 or 5–10 years before earliest known breast cancer in family[c]	Yearly
Women ≥ 35 with a 5-year Gail model risk of 1.7% or higher	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	Age identified as being at increased risk by Gail model	Every 6–12 months
	Mammography (consider tomosynthesis)	Age identified as being at increased risk by Gail model	Yearly
		If treatment would not occur	Yearly
Women with a lifetime risk > 20% because of LCIS or ADH/ALH	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b])	At diagnosis of LCIS or ADH/ALH	Every 6–12 months
	Mammography (consider tomosynthesis)	At diagnosis of LCIS or ADH/ALH but before age 30	Yearly
	Consider MRI	At diagnosis of LCIS or ADH/ALH but not before age 25	Yearly
Women with lifetime risk > 20% on family history risk models	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE[b,d])	Age identified as being at increased risk	Every 6–12 months
	Mammography (consider tomosynthesis)	Beginning 10 years before youngest family member but not before age 30	Yearly
	Consider MRI	Beginning 10 years before youngest family member but not before age 25	Yearly

Prior thoracic radiation therapy at age 10–30 years and current age ≥ 25	Clinical encounter (ongoing risk assessment, risk reduction counseling, CBE)	Beginning 8–10 years after radiation therapy	Every 6–12 months[e]
	Mammography (consider tomosynthesis)	Beginning 8–10 years after radiation therapy but not before age 25	Yearly
	Consider MRI	Beginning 8–10 years after radiation therapy but not before age 25	Yearly

[a]All patients should be familiar with breast awareness and should promptly report any changes.
[b]Consider risk reduction strategies
[c]Age > 75, individualize screening.
[d]Refer for genetic counseling.
[e]If current age ≤ 25, perform yearly.
ADH = atypical ductal hyperplasia; ALH = atypical lobular carcinoma; CBE = clinical breast examination; LCIS = lobular carcinoma in situ; PTHS, phosphatase and tensin homolog (*PTEN*) Hamartoma tumor syndrome.
Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, version 1. 2015; and National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer, version 1. 2017.

a microscope, whereas liquid-based cytology is a collection of cells placed in a vial containing a liquid medium that is processed by a laboratory into a cell thin layer, stained, and examined by light microscopy. These methods are thought to be equivalent in detecting positive findings, according to two randomized trials (Moyer 2012a). Human papillomavirus testing is also done by collecting cells from the endocervix by a spatula or brush. One of the available HPV tests detects the presence or absence of high-risk HPV types (i.e., 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 68, 69, 82), whereas the other tests report the presence or absence of HPV 16 and 18, which are associated with high-grade cancers. No specific HPV test is recommended by the guideline, but the test should conform to current standards for well-validated HPV DNA tests (Saslow 2012).

Screening Guidelines for Normal-Risk Patients

The ACS, American Society of Colposcopy and Cervical Pathology, American Society for Clinical Pathology, USPSTF, and ACOG have published guidelines for cervical cancer screening (ACOG 2016; Moyer 2012a; Saslow 2012). Each of these guidelines recommends that cervical cancer screening begin at age 21, with cervical cytology (e.g., Pap smear) every 3 years. When women reach age 30, they may wish to lengthen the screening interval and thus may have cervical cytology and HPV testing, often called "co-testing," every 5 years. At age 65, if the woman has no history of moderate or severe cervical dysplasia or cancer, has had three consecutive negative Pap smears or two consecutive co-test results within the past 10 years, and has had cervical cancer screening within the past 5 years, she may stop screening. Women who have had a hysterectomy with removal of the cervix and no history of high-grade cancerous lesions no longer need to have cervical cancer screening. However, if the hysterectomy does not remove the entire cervix or the patient has a history of high-grade precancerous lesions, continued cervical cancer screening should occur. Prior HPV vaccination does not change the recommendations for cervical cancer screening because the vaccine is not completely effective in preventing cervical cancer. Controversy exists over continuing annual pelvic examinations. In 2014, the American College of Physicians (ACP) released guidelines recommending against annual pelvic examinations in healthy, low-risk women because these women do not meet the criteria for effective screening procedures (Qassem 2014). However, the ACOG recommends annual pelvic examinations with a speculum and bimanual examinations for women older than 21 because they not only assist in identifying malignancies, but may also assist in recognizing incontinence and sexual dysfunction (Burns 2015).

Screening Guidelines for High-Risk Patients

Patients at a high risk of developing cervical cancer need more intensive or alternative screening. These include women with a history of precancerous cervical cancer, those with in utero exposure to diethylstilbestrol, and those who are immunocompromised (e.g., HIV, or long-term corticosteroid use) (Saslow 2012). The optimal screening tests and frequency in these populations are unknown, and existing guidelines do not specifically address all high-risk populations. Women with a history of precancerous lesions should initially have cervical cytology and HPV co-testing 12 and

24 months after treatment. If both tests are negative, co-testing should be repeated in 3 years; then, if negative again, the patient can begin regular cervical screening recommendations for normal-risk patients for a minimum of 20 years, even if this extends beyond age 65 (Massad 2013). Daughters of women exposed to diethylstilbestrol should have annual screening that continues until they are no longer a candidate for treatment if cervical cancer is diagnosed, such as if they have comorbidities that preclude the safe administration of treatment. The Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents recommends that patients with HIV begin screening at the time of sexual activity but no later than age 21 and continue throughout the woman's life (Panel on Opportunistic Infections 2015). Annual screening with cervical cytology is recommended in women younger than 30; once they have three consecutive negative tests, the screening interval can be extended to every 3 years. Women with HIV-positive infection who are 30 and older can be screened with cervical cytology or co-testing annually. Again, if three consecutive negative tests occur, the screening interval can be extended to 3 years. Women with other immunocompromised diseases are advised to follow these recommendations because no specific studies or society recommendations exist.

Colorectal Cancer

Patients with localized CRC have a 91% 5-year survival rate, whereas those with advanced or distant disease have a 72% 5-year survival rate, showing that an earlier diagnosis can affect survival (NCCN 2015a). Furthermore, 63% of CRC deaths are attributed to non-screening.

Types of Screening Methods

Colorectal cancer screening can be completed using structural or fecal-based tests. Structural tests can detect both early cancer and polyps using either endoscopic imaging (i.e., colonoscopy, flexible sigmoidoscopy) or radiologic imaging (i.e., virtual colonoscopy, flexible sigmoidoscopy, CT colonography). Colonoscopy uses an endoscope to fully examine the entire large bowel, including the cecum in most patients, and allows for simultaneous removal of premalignant lesions (i.e., polyps). Flexible sigmoidoscopy uses a 60-cm flexible sigmoidoscope to examine the lower half of the bowel to the splenic flexure for most patients. The CT colonography or virtual colonoscopy is an imaging procedure that creates two- and three-dimensional images of the colon using CT scans. Lesions suggestive of cancer found during CT colonography or flexible sigmoidoscopy require further evaluation/removal by colonoscopy. Therefore, colonoscopy is considered the gold standard for CRC screening.

Fecal tests detect signs of CRC in stool samples: occult blood (i.e., fecal occult blood tests) or alterations in exfoliated DNA (i.e., stool DNA test) that may be associated with bleeding adenomas or cancer. Guaiac-based fecal occult blood tests (gFOBTs) detect peroxidase activity of heme when hemoglobin comes in contact with a guaiac-impregnated paper (Levin 2008). Typically, the patient will require three consecutive bowel movement samples with gFOBT (Box 1-2). A small amount of feces is smeared on the kit's paper and covered with the provided kit. When hydrogen peroxide is dropped onto the paper with feces, a blue color appears if trace amounts of blood are present. False-negative and false-positive results can occur with certain diets and medications (Box 2).

Fecal immunochemistry tests (FITs) were developed to reduce false-negative and false-positive results associated with gFOBT. These tests use antibodies to detect globulin protein in hemoglobin when it is present in stool. Because globulin is degraded by enzymes in the upper GI tract, it is more specific for lower GI bleeding. The patient collects a small amount of feces using a probe provided in the kit and mails it to a laboratory for processing. Unlike gFOBT, the FIT does not require dietary restrictions and only requires a single stool sample annually.

DNA screening tests use molecular-screening strategies to detect elevated concentrations of altered DNA and/or hemoglobin, which may be present in feces. As in the FIT test, the patient collects a small amount of feces using a probe

Box 1-2. Causes of False-Negative or False-Positive Guaiac-Based Fecal Occult Test Results

False Positives

Dietary

- Consumption of red meat (beef, lamb, liver) and raw vegetables with peroxidase activity (turnips, broccoli, cauliflower, and radishes) within 3 days before testing[a]

Medical

- Rectal enemas, rectal medications, and digital rectal examination within 3 days before testing
- Aspirin or NSAIDs within 7 days before testing
- Testing if blood from hemorrhoids is present in stool
- Testing if within 3 days of menstrual activity

False Negatives

Dietary

- Consumption of vitamin C in excess of 250-mg supplements or from citrus fruits or juices within 3 days before testing

Medical

- Testing dehydrated samples

[a]Test instructions for several products no longer contain dietary vegetable or fruit restrictions.

Information from: Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008; a joint guideline from the American Cancer Society, the US Multi-Society on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:138-60.

provided in the kit and sends a full bowel movement sample to a laboratory for processing. Like FIT, DNA screening also does not require dietary restrictions and requires only a single stool sample. However, the optimal interval for screening is unknown at this time. Benefits and limitations of each screening method are described in Table 1-4.

Screening Guidelines for Normal-Risk Patients

Men and women 50 and older with no history of adenomas, polyps, or inflammatory bowel disease (e.g., ulcerative colitis, Crohn disease) and no family history (e.g., none or only distant relatives) of CRC are considered at an average risk of developing CRC (NCCN 2015a). The ACS, NCCN, USPSTF, and

Table 1-4. Benefits and Limitations of Available CRC Screening Methods

Screening Method	Benefits	Limitations
Structural Examinations		
Colonoscopy	• View entire colon • Most sensitive screening method • Can remove polyps • Few complications	• Full bowel preparation required • Can be expensive • Sedation and chaperone required • Highest bowel tear/perforation rate • Requires missed day of work
CT colonography	• Examines entire colon • High sensitivity and specificity for moderate-large adenomas • Fairly quick • Few complications • No sedation needed • Noninvasive	• Full bowel preparation required • Cannot remove polyps • Low-dose radiation exposure • Colonoscopy required if abnormalities • Not covered by all insurers
Flexible sigmoidoscopy	• Few complications • No sedation needed	• Views only one-third of colon • Cannot remove large polyps • Small risk of infection or perforation • Slightly more effective than FOBT at detecting CRC • Colonoscopy required if abnormalities • Limited availability
Fecal Tests		
DNA test	• No bowel preparation needed • Sampling done at home • Requires only a single stool sample • No sedation needed • Noninvasive	• Will miss most polyps • High cost compared with other fecal tests • New technology with uncertain testing interval • Colonoscopy necessary if abnormal
Fecal immunochemistry test (FIT)	• No bowel preparation needed • Sampling done at home • Requires only a single stool sample • Low cost • No sedation needed • Noninvasive	• Will miss most polyps • May produce false-positive results • Slightly more effective at detecting CRC when done in combination with sigmoidoscopy at 5 years • Colonoscopy necessary if abnormal • Requires multiple stool samples
Guaiac-based fecal occult test (FOBT)	• No bowel preparation needed • Sampling done at home • Low cost • No sedation needed • Noninvasive	• Requires pretest dietary and medication limitations • Requires multiple stool samples • Will miss most polyps • May produce false-positive results • Slightly more effective at detecting CRC when done in combination with sigmoidoscopy at 5 years • Colonoscopy necessary if abnormal

CRC = colorectal cancer.

Information from: American Cancer Society (ACS). Colorectal Cancer Facts & Figures 2014–2016. Atlanta: ACS, 2014.

Table 1-5. CRC Screening Recommendations for High-Risk Patients

High-Risk Patient Type	Recommendation
Family History	
One first-degree relative with CRC diagnosed before age 60 or two first-degree relatives with CRC diagnosed at any age	Begin CRC screening with colonoscopy every 5 years beginning 10 years before the earliest family member's diagnosis age or at age 40 at the latest
One first-degree relative with CRC diagnosed at age 60 and older or one second-degree relative with CRC diagnosis at younger than 50	Begin CRC screening with colonoscopy at age 50 but may have screening interval shortened to every 5–10 years
One or more first-degree relative with an advanced adenoma	Begin CRC screening with colonoscopy every 5–10 years at age of onset of advanced adenomas diagnosis in their relative or at age 50 at the last test
Personal History	
Inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis)	Begin CRC screening using a colonoscopy every 1–2 years 8–10 years after symptom onset
High-risk familial syndromes (e.g., Lynch, polyposis, Cowden, and Li-Fraumeni syndromes)	Refer for genetics counseling at a cancer center that is well equipped to handle appropriate screening, diagnosis, and treatment

Information from: National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, version 1. 2015.

American College of Gastroenterology all have guideline recommendations for CRC screening (NCCN 2015a; Smith 2015; Rex 2009; USPSTF 2008). Each of these guidelines recommend that beginning at age 50, men and women be screened for CRC. The American College of Gastroenterology suggests that African Americans should begin screening at age 45 (Rex 2009). The only guideline that recommends when to stop screening for CRC is the USPSTF, which recommends against routine screening for patients older than 75 (USPSTF 2008). Each guideline recommends colonoscopy screening every 10 years, gFOBT or FIT annually, or flexible sigmoidoscopy with or without gFOBT (or FIT, according to the ACS and the NCCN) every 5 years. In addition, the ACS recommends a CT colonography every 10 years and stool DNA testing without a recommended frequency (Smith 2015).

Screening Guidelines for High-Risk Patients

Patients with high-risk features include those with a family history of CRC, inflammatory bowel disease, or high-risk syndromes (e.g., Lynch, polyposis, Cowden, and Li-Fraumeni syndromes). The screening guidelines for these patients are more aggressive and are detailed in Table 1-5 (NCCN 2015a).

Lung Cancer

Lung cancer is the leading cause of mortality worldwide (NCCN 2016c), despite having an incidence similar to other common cancers like breast, colorectal, and prostate cancer. This discrepancy has been attributed to the fact that screening programs for these other cancers have been in place for decades. Recommendations for routine screening for lung cancer are relatively new, with the first guidelines introduced in 2011.

Types of Screening Methods

Initial lung cancer-screening trials evaluated the use of chest radiographs to improve lung cancer survival. However, most of these studies had flawed study designs and insufficient power, and none showed a benefit in lung cancer diagnoses or mortality (NCCN 2016c). More recently, studies have evaluated low-dose CT lung cancer screening. Low-dose CT delivers 20% of the radiation dose as conventional CT, yet there is comparable sensitivity and specificity for lung nodule detection with this method (Sharma 2015). The relative risk of lung-cancer mortality significantly decreases (RR, 20%; 95% CI, 6.8-26.7; p=0.004) with the use of low-dose CT screening in patients at risk of lung cancer (NCCN 2016c).

Screening Guidelines for Patients at Risk

The American College of Chest Physicians, ACS, NCCN, and USPSTF provide guidelines on the screening for patients with lung cancer at risk (NCCN 2016c; Moyer 2014; Detterbeck 2013; Wender 2013). These organizations all recommend that patients 55 and older with no signs of lung cancer be assessed for smoking history. Those who have at least a

30 pack-year smoking history, who currently smoke, or who have quit within the past 15 years and are in good health should be considered for lung cancer screening. The NCCN also recommends that patients 50 and older with a 20 pack-year or more history of smoking and one additional risk factor (i.e., occupational exposure to carcinogens, residential radon exposure, history of cancer, family history of lung cancer, and/or history of lung disease) be considered for lung cancer screening (NCCN 2016c).

The decision to screen for lung cancer, however, should be a shared health care provider/patient decision after a discussion of the benefits and risks of screening. Benefits of screening include (1) decreased lung cancer mortality or improvement of other oncologic outcomes; (2) improved quality of life; and (3) detection of other lung diseases that require treatment. Risks of screening include (1) false-positive results leading to unnecessary tests, invasive procedures, cost, and psychological distress; (2) false-negative results, which may delay or prevent diagnosis and treatment; (3) detection of aggressive tumors that do not alter overall survival; (4) overdiagnosis resulting in unnecessary treatment; (5) indeterminate results requiring further testing; (6) radiation exposure; and (7) physical complications from diagnostic workup (NCCN 2016c). If the provider and the patient agree to begin lung cancer screening with annual low-dose CT scans, the decision to stop routine screening differs, depending on the guideline. The exact benefit of lung cancer screening beyond age 75–80 is unknown because the original trials evaluating lung cancer screening only included individuals age 50–70 or 75, depending on the trial. The American College of Chest Physicians, ACS, and NCCN recommend to stop screening at age 75 or if the patient is no longer eligible for lung cancer treatment because of comorbidities/preference (NCCN 2016c; Moyer 2014; Detterbeck 2013; Wender 2013). The USPSTF guidelines recommend to stop screening at age 80 or when a person has not smoked for 15 years (Moyer 2014).

Patient Care Scenario

A 52-year-old woman who recently emigrated from Bolivia is in your primary care clinic for the first time this week. Her medical history is significant for obesity and osteoarthritis. She has a 34 pack-year history of smoking and currently is trying to quit but denies alcohol use. She has no significant family history for cancer. She is single and has no children. You have been charged with developing a cancer-screening plan for this patient.

ANSWER

The first step is to identify the types of cancer screening the patient is eligible for and whether your institution follows specific guidelines for cancer screening. The NCCN has recommendations for each of these cancers that are updated at least annually, whereas other professional societies have guidelines that may be updated less often. The guideline that your institution selects is an individual choice. The most important aspect is to be sure you access the most recent guideline recommendations.

As a woman, this patient is at risk of developing breast, cervical, colorectal, endometrial, lung, ovarian, and skin cancer. To determine the appropriate type of screening, a risk factor assessment will need to be completed for each type of cancer. The patient has no known mutations for *BRCA1* or *BRCA2*, nor does she have a history of therapeutic thoracic radiation therapy or genetic syndrome; thus, she is at an average risk of breast cancer. Screening with mammography is recommended in all of the recommended guidelines for a woman age 52 every 1–2 years (ideally beginning at age 40–50 years, depending on the guideline). Similarly, this patient is at an average risk of developing cervical cancer because she has no precancerous cervical cancer and no exposure in utero to diethylstilbestrol and is not immunocompromised. Therefore, screening with cervical cytology and HPV testing at least every 5 years is recommended. This patient is also at an average risk of developing CRC because she has no family history of CRC, inflammatory bowel disease, or high-risk syndromes. Therefore, CRC screening should begin immediately (age 50, ideally). Selection of CRC screening method may depend on patient and provider preference. The gold standard screening method is colonoscopy because it can be used to screen for and remove polyps and adenoma (preventing CRC development). If colonoscopy is chosen, it should be done every 10 years. Alternatives include gFOBT and FIT yearly or flexible sigmoidoscopy with or without gFOBT or FIT every 5 years. Because this woman is a smoker, she should be considered for lung cancer using low-dose CT scans annually. Screening guidelines are not currently available for endometrial or ovarian cancer. The patient could be educated about risks and symptoms of endometrial cancer when she goes through menopause and self-skin checks for skin cancer.

1. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;156:880-91.
2. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Breast Cancer Screening and Diagnosis, 2015.
3. NCCN Clinical Practice Guidelines in Oncology. Colorectal Cancer Screening, 2015.
4. NCCN Clinical Practice Guidelines in Oncology. Lung Cancer Screening, 2016.

Prostate Cancer

In 2015, prostate cancer mortality rates were reduced by almost one-half from their highest rates because of early detection through cancer-screening programs and improved treatment (Siegal 2015).

Types of Screening Methods

Prostate-specific antigen is a glycoprotein that is secreted by prostatic epithelial cells and that enhances sperm motility. It can enter the bloodstream; the normal range is 4–10 ng/mL (NCCN 2016b). Prostate-specific antigen is not a prostate cancer–specific marker, and elevated concentrations may be caused by benign prostatic hyperplasia, prostatitis, or instrumentation of the prostate. However, PSA is used for prostate cancer screening because screening has survival benefits. At a PSA cutoff of 3.1 ng/mL, PSA has a sensitivity of 32% and a specificity of 87% (Thompson 2013). The PSA concentrations can be elevated because of infection, recent instrumentation, ejaculation, or trauma (NCCN 2016b). Conversely, 5-α-reductase inhibitors (e.g., dutasteride, finasteride), when used to treat benign prostatic hyperplasia, and ketoconazole, which inhibits androgen synthesis, can decrease PSA concentrations. Herbal supplements such as saw palmetto can affect PSA, but little is known about the exact effects. Therefore, it is always recommended to obtain a thorough medication history when evaluating PSA concentrations.

Digital rectal examination is a manual examination technique in which the health care provider inserts a gloved finger into the rectum and then palpates the prostate through the rectal wall. Prostate gland size, shape and consistency, and mobility can be noted during a DRE. The positive predictive value of this examination is poor (4%–11%); therefore, as a solo screening test, it is not recommended (Schröder 1998; Flanigan 1994). If a DRE is used, it should be combined with PSA testing.

Screening Guidelines for Normal-Risk Patients

The ACS, American Urology Association (AUA), ACP, NCCN, and USPSTF all have guidelines for prostate cancer screening (Carter 2016; NCCN Prostate Cancer Early Detection 2016; Qaseem 2013; Wolf 2010). Each of these societies, except for the USPSTF, recommends beginning a conversation about the risks and benefits of prostate cancer screening in men at age 45 (NCCN), 50 (ACP and ACS), or 55 (AUA) (Carter 2016; NCCN Prostate Cancer Early Detection 2016; Qaseem 2013; Wolf 2010). The USPSTF recommends against PSA-based routine screening in men without symptoms because the reduction in prostate cancer mortality is very small and the harms of screening (pain, fever, infection, transient urinary difficulties associated with prostate biopsy) and prostate cancer treatment (e.g., erectile dysfunction, urinary incontinence, bowel dysfunction, premature death) may outweigh the benefit of detecting prostate cancer in asymptomatic men (Moyer 2012b). The ACP, ACS, AUA, and NCCN recommend PSA testing. The NCCN also recommends considering a baseline DRE. The frequency of testing depends on the guidelines, but essentially, all recommend repeating PSA every 1–4 years, depending on PSA concentration, and screening should not continue in patients with a life expectancy of less than 10–15 years (or typically around age 70–75 for most men) (Table 1-6).

Table 1-6. Prostate Cancer-Screening Guidelines

Organization	Initiation	Cessation	Frequency
American Cancer Society	Age 50 with life expectancy > 10 years	Asymptomatic with life expectancy < 10 years	Every 1–2 years, depending on PSA concentration
American College of Physicians	Age 50	Age 70 with life expectancy < 10–15 years	Every 1–4 years; every year if PSA ≥ 2.5 ng/mL
American Urological Association	Age 55	Age 70 or men with life expectancy < 10–15 years	Every 2 years or more, if preferred
National Comprehensive Cancer Network	Age 45	Age 75; may continue in select patients	Every 1–4 years, depending on PSA concentration
U.S. Preventive Services Task Force	Recommends against PSA-based screening for men without symptoms		

PSA = prostate-specific antigen.

Information from: Qaseem A, Berrty MJ, Denberg TD, et al. Screening for prostate cancer: a guidance statement from the clinical guidelines committee of the American College of Physicians. Ann Intern Med 2013;158:761-9; Carter HB, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. American Urological Association, 2016; National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Prostate Cancer Screening, 2016; Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157:120-34; and Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer; Update 2010. CA Cancer J Clin 2010;60:70-98.

Screening Guidelines for High-Risk Patients

African American men with a first-degree relative with prostate cancer, particularly when it is diagnosed at a younger age, are at a higher risk of prostate cancer (about 2-fold) (NCCN 2016b). Several organizations, including ACP, ACS, and AUA, recommend that high-risk patients begin prostate cancer screening at age 40–45 (Carter 2016; Qaseem 2013; Wolf 2010). Other organizations, such as the USPSTF and NCCN, however, do not recommend different screening guidelines for high-risk patients (NCCN 2016b; Moyer 2012). This is because the effects of earlier treatment or more intensive screening in these patients are not apparent. The large prostate cancer-screening trials that showed the benefit of screening often either had small populations of high-risk patients (e.g., Prostate, Lung, Colorectal and Ovarian Trial, 4.4% African Americans; 6.9% of the patients enrolled had a positive family history) or no data on race or family history. Therefore, the NCCN panel currently states that evidence is insufficient to recommend different screening recommendations, but these individuals should be monitored closely for adherence to screening. Thus, patients with a high-risk feature, such as African American race or family history, should engage in a thorough discussion with their health care providers about the risks and benefits of beginning prostate cancer screening earlier than age 45.

Practice Points

- **Cancer prevention and screening can prevent many cancers and detect precancerous or early-stage cancers, significantly reducing morbidity and mortality. Developing an appropriate cancer screening and, if appropriate, prevention plan, should be part of routine preventive care medicine.**
- **Cancer prevention strategies are available for women who have the *BRCA1* and/or *BRCA2* mutation or other high-risk features.**
- **Low-dose aspirin (75–100 mg by mouth daily or 100–325 mg by mouth every other day) is recommended for adults age 50–59 with a life expectancy of at least 10 years and not at risk of bleeding to prevent CRC; adults age 60–69 may also benefit.**
- **Polyps should be removed, when detected, to prevent CRC development.**
- **The HPV vaccine should be administered to boys and girls, men age 22–26 who have sex with men, and adults age 22–26 who are immunocompromised, to prevent HPV-related cancers, according to the 2016 CDC Advisory Committee on Immunization Practices guidelines.**
- **Routine cancer-screening recommendations are available for breast, cervical, CRC, lung, and prostate cancer in both patients at average risk and those at high risk.**
- **Guidelines may differ in their recommendations, and the most recent guidelines should be consulted when developing a patient-specific cancer-screening plan.**

Other Cancer Screening

Endometrial Cancer Screening for High-Risk Patients

Currently, no screening tests are available for endometrial cancer. The ACS, however, does recommend that when a woman undergoes menopause, she be educated about the risks and symptoms of endometrial cancer and immediately report any vaginal bleeding, discharge, or spotting (Smith 2001). In addition, women at an increased risk of endometrial cancer, including those who have never given birth; have infertility, diabetes, or hypertension; or have taken estrogen or tamoxifen therapy, should be educated on reporting abnormal vaginal bleeding promptly. Moreover, women with hereditary nonpolyposis colon cancer (often called Lynch syndrome) are at a high risk of endometrial cancer. These women should receive an annual endometrial biopsy beginning at age 35.

Skin Cancer-Screening Recommendations

Skin cancer is the most commonly diagnosed cancer in the United States. In the past, it was recommended that health care providers regularly perform a full-body skin examination. Despite this, randomized clinical trials have not examined whether screening improves outcomes such as reduced morbidity and mortality of skin cancer (USPSTF 2009). Therefore, the USPSTF recommends against any routine skin cancer screening. The American Academy of Dermatology promotes skin cancer screening through regular skin self-examinations for all individuals and offers free cancer screenings throughout the year. Patients with a history of skin cancer or melanoma should receive more regular screening by a dermatologist.

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

K.G. is a 58-year-old white man in the clinic for a medication therapy management follow-up visit. His primary care physician has recommended colorectal cancer (CRC) screening, but K.G. recently read a news article about drugs to prevent CRC. K.G. wants your advice about the screening and prevention methods. K.G.'s medical history includes hyperlipidemia, hypertension, and coronary artery disease; he is a nonsmoker. His home drugs include simvastatin 20 mg by mouth at bedtime and hydrochlorothiazide 25 mg by mouth daily. K.G.'s blood pressure today is 158/78 mm Hg, and his fasting lipid panel results are TC 200 mg/dL and HDL 30 mg/dL.

1. Which one of the following best justifies recommending CRC screening in K.G.?

   A. Reduces risk factors.
   B. Identifies cancerous lesions for removal.
   C. Identifies cancers at an early stage.
   D. Alters carcinogenesis.

2. Which one of the following is the best colorectal screening option to recommend for K.G.?

   A. Colonoscopy every 5 years
   B. CT colonography every 5 years
   C. Fecal immunochemistry test (FIT) annually
   D. Guaiac-based fecal occult blood test (gFOBT) every 3 years

3. Which one of the following CRC prevention therapies is best to recommend for K.G.?

   A. Aspirin 81 mg by mouth daily
   B. Celecoxib 200 mg by mouth daily
   C. Ibuprofen 200 mg by mouth daily
   D. Sulindac 150 mg by mouth daily

Questions 4 and 5 pertain to the following case.

M.T. is a 54-year-old African American woman with obesity. Her family history is positive for her father given a diagnosis of CRC at age 58. M.T.'s medical history is significant for diabetes and hypertension. She consumes 1 or 2 alcoholic drinks per day. M.T. had her first menstrual period at age 10 years, and she was 22 years when she had her daughter.

4. Which one of the following breast cancer prevention strategies is best to recommend for M.T.?

   A. Anastrozole 1 mg orally daily x 5 years
   B. Bilateral mastectomy
   C. Tamoxifen 20 mg orally daily x 5 years
   D. No preventive therapy recommended

5. Which one of the following would be the optimal age for M.T. to begin CRC screening?

   A. 30 years
   B. 40 years
   C. 50 years
   D. 55 years

Questions 6–8 pertain to the following case.

L.D. is a 32-year-old white woman whose mother and sister both died of breast cancer before age 50. Genetic testing shows that L.D. is *BRCA2* positive. She has two daughters (age 6 and 4 years). L.D.'s social history is significant only for a 20 pack-year history of smoking.

6. Which one of the following breast cancer prevention strategies is most likely to reduce L.D.'s risk of developing breast cancer by 90%?

   A. Anastrozole 1 mg orally daily x 5 years
   B. Bilateral mastectomy
   C. Bilateral salpingo-oophorectomy
   D. Tamoxifen 20 mg orally daily x 5 years

7. Which additional cancer-screening test is best to recommend for L.D.?

   A. Cervical cancer
   B. CRC
   C. Endometrial cancer
   D. Lung cancer

8. L.D. wishes to have more children but is concerned about her risk of developing ovarian cancer. Which one of the following options would best decrease L.D.'s risk of ovarian cancer while preserving her ability to conceive?

   A. Anastrozole 1 mg orally daily x 10 years
   B. Bilateral salpingo-oophorectomy
   C. Ethinyl estradiol 20 mcg/drospirenone 3 mg orally daily x 21 days every 28 days
   D. Tamoxifen 20 mg orally daily x 10 years

9. A 19-year-old man with HIV infection comes to the clinic. Which one of the following educational points about the 9-valent human papillomavirus (HPV) vaccine is best to give this patient?

   A. It protects against anal cancer and genital warts.
   B. It protects against anal and oropharyngeal cancer.
   C. It protects against anal and penile cancer and genital warts.
   D. It protects against anal, penile, and oropharyngeal cancer.

10. According to the latest immunization guidelines, an 11-year-old African American boy should receive the 3-injection series of the HPV vaccine. Which one of the following vaccines is best to recommend for this patient?

    A. Bivalent
    B. Quadrivalent or 9-valent
    C. Any of the three: bivalent, quadrivalent, or 9-valent
    D. Bivalent or quadrivalent

Questions 11–13 pertain to the following case.

L.P. is a 55-year-old Asian American woman with a 38 pack-year smoking history. Her pertinent medical history includes hypertension and a hysterectomy with removal of cervix. L.P.'s home drugs include amlodipine. She has a 5-year cumulative breast cancer risk of 1.5%.

11. After discussing risk-benefit with her health care provider, which one of the following is best to recommend for L.P.?

    A. Breast cancer screening with breast MRI yearly
    B. Lung cancer screening with low-dose CT scan yearly
    C. Skin cancer screening with annual health care provider skin examinations
    D. Cervical cancer screening with Pap smear and HPV test every 3 years

12. L.P. is eligible for CRC screening beginning at age 50. Which one of the following CRC screening tests is best to recommend for L.P.?

    A. Colonoscopy every 10 years
    B. CT colonography every 5 years
    C. FIT every 5 years
    D. Flexible sigmoidoscopy every 10 years with or without sensitive gFOBT

13. L.P. wishes to decrease her risk of breast cancer and CRC. She asks you about whether medications can prevent breast cancer or CRC. Which one of the following best answers L.P.'s question?

    A. Aspirin 81 mg by mouth daily for CRC prevention and no preventive therapy for breast cancer.
    B. Aspirin 81 mg by mouth daily for CRC prevention and tamoxifen 20 mg by mouth daily for breast cancer prevention.
    C. No preventive therapy for CRC and tamoxifen 20 mg by mouth daily for breast cancer prevention.
    D. No preventive therapy for either CRC or breast cancer.

14. A 50-year-old healthy Asian man asks your recommendation for cancer screening. Because his brother had complications with prostate cancer screening (false-positive results, incontinence after biopsy), the patient has concerns. Which one of the following guideline recommendations seems most reasonable in this patient?

    A. Begin annual digital rectal examination (DRE) screening now, according to the ACS guidelines.
    B. Begin annual prostate-specific antigen (PSA) screening now, according to the AUA guidelines.
    C. Begin biannual PSA plus annual DRE screening, according to the NCCN.
    D. No prostate cancer screening is recommended, according to the USPSTF guidelines.

15. A 55-year-old white woman has no risk factors for breast cancer other than age and sex. She is a self-employed housekeeper and finds yearly mammography difficult to schedule and a hardship to pay for. So far, she has had no positive mammography findings. According to national guidelines, which one of the following is the most appropriate frequency of mammography to recommend for this patient?

    A. Yearly
    B. Every 2 years
    C. Every 5 years
    D. Only if symptoms develop

16. A 42-year-old premenopausal white woman has a family history that includes her mother and two maternal aunts dying of breast cancer at 70–80 years of age. Her 54-year-old sister was recently given a diagnosis of breast cancer. The patient's genetic testing did not reveal a *BRCA1* or *BRCA2* mutation; however, her calculated 5-year breast cancer risk is 2%. She has no other pertinent medical history, and her only medication is a levonorgestrel-releasing intrauterine device. Which one of the following breast cancer prevention strategies is best to recommend for this patient?

    A. Anastrozole 1 mg orally daily x 5 years
    B. Bilateral mastectomy
    C. Raloxifene 60 mg orally daily x 5 years
    D. Tamoxifen 20 mg orally daily x 5 years

17. A 63-year-old white man has a 45 pack-year history of smoking but quit smoking 13 years ago. His medical history is significant for benign prostatic hyperplasia, hypercholesterolemia, and hypertension. He has been receiving low-dose CT lung cancer screening for the past 5 years, all with negative results. Which one of the following is the best time for this patient to stop lung cancer screening?

    A. Now, after 5 years of negative results because exact benefit beyond this is unknown
    B. Age 80 because exact benefit after this age is unknown
    C. Age 83 after 10 years of negative results because exact benefit beyond this is unknown
    D. Age 70 because that is the upper age limit of patients enrolled in studies

18. A 59-year-old African American woman with obesity is evaluated for hypertension in a follow-up at your clinic. Her medical history is significant for cataracts, osteoporosis, diabetes, and hypertension. She began menses at age 11 years and had her first child at 19 years. Her family history is positive for a maternal grandmother with breast cancer. Because a friend received a diagnosis of breast cancer at age 55, the patient asks how to best decrease her own risk of breast cancer. Which one of the following is best to recommend for this patient?

    A. Exemestane 25 mg orally daily
    B. Tamoxifen 20 mg orally daily
    C. Raloxifene 60 mg orally daily
    D. Weight reduction through exercise and dietary changes

Questions 19 and 20 pertain to the following case.

L.M. is a 39-year-old African American man with a family history that includes his father dying of prostate cancer at age 70. L.M. is healthy now but is interested in prostate cancer prevention and screening.

19. Which one of the following is best to recommend for L.M. to decrease his risk of prostate cancer mortality?

    A. Lycopene 15 mg orally daily
    B. Dutasteride 0.5 mg orally daily
    C. Finasteride 5 mg orally daily
    D. No chemoprevention therapy

20. Which one of the following is the best time and prostate cancer-screening method to recommend for L.M.?

    A. DRE beginning at age 45
    B. DRE beginning at age 50
    C. PSA beginning at age 45
    D. PSA beginning at age 50

Learner Chapter Evaluation: Cancer Screening and Prevention.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Evaluate the risks and benefits of cancer screening and prevention.
13. Assess the differences in cancer prevention therapies for patients with normal- and high-risk breast cancer.
14. Construct a cancer prevention plan for a patient at risk of breast, colorectal, human papillomavirus–related, or prostate cancer.
15. Distinguish between cancer screening guideline recommendations for breast, cervical, colorectal, lung, and prostate cancers.
16. Design an appropriate cancer-screening plan for an individual patient according to cancer-screening guidelines and individual risk factors.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Lung Cancer

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LEARNING OBJECTIVES

1. Design a treatment plan for a patient with small cell lung cancer.
2. Evaluate the role of mutational analysis in patients with non–small cell lung cancer (NSCLC).
3. Design a treatment plan for a patient with NSCLC.
4. Develop a treatment algorithm for a patient with metastatic NSCLC with epidermal growth factor receptor mutation–positive disease, anaplastic lymphoma kinase rearrangement, or ROS proto-oncogene 1 rearrangement.
5. Assess the impact of adding vascular endothelial growth factor receptor inhibitors in NSCLC.
6. Examine the role of immunotherapy in the treatment of metastatic NSCLC.

ABBREVIATIONS IN THIS CHAPTER

ALK	Anaplastic lymphoma kinase
EGFR	Epidermal growth factor receptor
IRAE	Immune-related adverse event
NSCLC	Non–small cell lung cancer
PCI	Prophylactic cranial irradiation
PD-1	Programmed cell death protein 1
PS	Performance status
ROS1	ROS proto-oncogene 1
SCLC	Small cell lung cancer
VEGF	Vascular endothelial growth factor

Table of other common abbreviations.

INTRODUCTION

Despite advances in treatment and detection, lung cancer remains the leading cause of cancer-related death in both women and men worldwide. Lung cancer can be divided into three subtypes: non–small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumors. Non–small cell lung cancer accounts for about 85% of all lung cancers, SCLC about 10%–15%, and lung carcinoid tumors about 5%. The initial pathological diagnosis is critical because the treatment approach differs greatly between the three subtypes. It is also imperative not only to distinguish the subtype, but also to further define the histology of the disease because this dictates the treatment approach and response. This chapter focuses on the diagnosis, staging, and management of the most common types of lung cancer, NSCLC and SCLC.

Prevalence and Incidence of Lung Cancer

In the United States, lung cancer is the second most common cancer diagnosis after prostate cancer in men and breast cancer in women. In 2016, the estimated incidence of new cases of lung cancer in the United States was estimated at over 224,000. Early detection programs are beginning to affect the time of diagnosis (and potentially, survival) in high-risk populations. In 2016, however, an estimated 158,000 deaths were attributable to lung cancer (Siegel 2016). Survival is directly correlated with the stage of disease, so patients with a diagnosis of early-stage disease have better outcomes than do patients with advanced or metastatic disease at diagnosis.

With the steady decrease in cigarette smoking in the United States since the early 1960s, the incidence and death rate from lung cancer have declined. Starting in the 1980s, the incidence and death rate as the result of lung cancer began to decline in men, and it continues to decrease. For women, both the incidence of lung cancer and death rate plateaued in the early 2000s and started to decline in 2003 (Siegel 2016). At the same time, certain subsets of NSCLC are emerging, such as NSCLC in never-smokers (a patient population who has smoked less than 100 cigarettes in their lifetime). Never-smokers account for 10%–15% of the NSCLC population and often have a molecular tumor profile different from smokers (Subramanian 2007).

Risk Factors for Developing Lung Cancer

The main risk factor for developing lung cancer is tobacco exposure. This can include cigarette, cigar, pipe smoking, and secondhand exposure. Both the number of cigarettes smoked and the duration of smoking affect the risk of developing lung cancer. Patients with the highest pack-year history are at highest risk of developing lung cancer. This could be up to a 30-fold increased risk over a never-smoker. Smoking cessation has helped reduce the incidence of lung cancer, but this result is only evident after many years. A U.S. veterans trial determined that the relative risk of lung cancer in former smokers compared with nonsmokers was 8-fold at 10 years of abstinence, which slowly declined to a relative risk of 2-fold over nonsmokers at 30 years (DeVita 2011). Additional risk factors include chronic obstructive pulmonary disease (COPD) and environmental or occupational exposures such as radon, asbestos, organic chemicals, radiation, and air pollution. The impact of genetic risk factors is an emerging area in lung cancer treatment. In younger patients, associated molecular aberrations are often likely the reason for developing lung cancer. Determination of these genetic changes and the impact on treatment is evolving. In general, the risk of lung cancer increases with age, with a peak during the seventh decade. This results in a lifetime probability of 1 in 13 for men and 1 in 16 for women (Siegel 2016; Li 2010; Peto 2000).

Etiology of Lung Cancer

Both NSCLC and SCLC develop from a series of mutational events and cellular abnormalities that arise from the bronchial epithelium. Proto-oncogenes are activated, leading to increased cellular proliferation, and tumor suppressor genes are inactivated, leading to resistance to programmed cell death. Malignant cells can acquire the ability to spread throughout the lymphatic system, metastasize to distant organs, and build new blood vessel formation by angiogenesis.

Small cell lung cancer is classified as a neuroendocrine tumor of the lung. The tumors tend to be centrally located and have rapid growth with a high mitotic rate. The incidence of small cell lung carcinoma has decreased to about 13% of lung cancers from a peak in the 1980s. This directly correlates with the increased emphasis on smoking cessation. Tobacco exposure is the cause of SCLC in over 95% of cases, which often present as a large central mass with hemoptysis. Small cell lung cancer is more aggressive than NSCLC, with a high proliferation rate revealed on pathology. This is evident by the large percentage of patients presenting with widespread metastatic disease and paraneoplastic diseases (DeVita 2011).

Non–small cell lung cancer is further classified according to the tumor histology, including squamous cell carcinoma, adenocarcinoma, and large cell neuroendocrine carcinomas. This classification is important because it commonly dictates the therapy selected. The relative incidence of these histologies has changed over the years. Historical epidemiology data support that smoking is most commonly associated with a squamous cell carcinoma histology in NSCLC. The decline in smoking has resulted in a subsequent decline in the incidence of squamous cell carcinoma histology and an increase in the incidence of adenocarcinoma.

Adenocarcinoma is the most common histology, accounting for 44% of all NSCLC cases (Charloux 1997). Adenocarcinoma tends to develop in smaller airways and the periphery of the lung. Squamous cell carcinomas, which account for 26% of NSCLC, are most often associated with smoking and commonly appear as a central mass in larger airways. Large cell carcinoma accounts for only about 15% of all lung cancer. Although often treated similarly to adenocarcinoma, it has a poorer overall prognosis (DeVita 2011).

Screening for Lung Cancer

With the high incidence of lung cancer and mortality from it, the development of screening techniques for early detection

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- The general knowledge of the mechanisms of action of chemotherapy and targeted therapy.
- The associated toxicities with chemotherapy and targeted therapy.

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- NCCN lung cancer guidelines
  - Non–small cell lung cancer
  - Small cell lung cancer
- American Cancer Society

is of utmost importance. The National Lung Screening Trial randomized 53,454 people to either low-dose screening CT scans or chest radiographs. Subjects were enrolled if they were 55–74 years of age and current or former smokers with at least a 30 pack-year history and no evidence of lung cancer. Screening with low-dose CT scans reduced lung cancer mortality by 62 deaths per 100,000 person-years, a relative risk reduction of 20% (Field 2012; Aberle 2011; Kramer 2011). More information about screening is available in the chapter on cancer screening and prevention.

Diagnosis of Lung Cancer

Signs and symptoms of lung cancer are often nonspecific and can be misinterpreted as an infection, pneumonia, or underlying lung disease such as COPD. Many patients are not symptomatic until they have an advanced stage of disease. About 60% of patients will present with a cough. Other symptoms include weight loss, dyspnea, chest pain, hemoptysis, and pneumonia. In metastatic disease, patients may have signs or symptoms from the affected organ such as a fracture from bone metastases or jaundice caused by hepatic involvement (DeVita 2011).

To diagnose lung cancer, a tissue biopsy to determine the histology and molecular testing to determine the presence of molecular mutations and gene rearrangements are vital. Patients will undergo either a CT or a PET (positron emission tomography) scan to determine the location of the primary tumor and the sites of spread or metastases. Patients who are at high risk of or are thought to have brain metastasis will undergo a brain MRI to determine the extent and location of spread (DeVita 2011).

SMALL CELL LUNG CANCER

The hallmarks of SCLC are its association with smoking, rapid tumor growth, and early metastatic disease. Because of the rapid growth of SCLC, patients are more likely to present with an advanced-stage or metastatic disease.

Staging of SCLC

Small cell lung cancer can be divided into two classifications according to the Veterans Administration Lung Study Group. Limited-stage SCLC is a tumor confined to the ipsilateral hemithorax that fits into the thoracic radiation field. Extensive-stage SCLC is a tumor that extends beyond the ipsilateral hemithorax or distant metastases. Because of the high incidence of brain metastasis, it is recommended that a brain MRI be done as part of the staging for SCLC (Siegel 2016; Kalemkerian 2013; Shepherd 2007; Micke 2002).

Although the veterans staging system is still used today, the American Joint Committee on Cancer updated its recommendations in 2010 to incorporate a staging system using tumor size, nodal involvement, and the presence of metastases (TNM). Patients can then be classified as having clinical stage I–IV disease, which is more predictive of overall survival than the veterans staging system (Kalemkerian 2013).

TREATMENT OF SCLC

Small cell lung cancer is a relatively chemosensitive disease. Because of its aggressiveness and tendency to spread quickly, surgery is not viable for most patients. This is mainly because of the high recurrence rate and likely presence of metastatic spread at diagnosis. The median overall survival for patients with limited-stage SCLC is reported as 17–26 months and decreases to 3–12 months for extensive-stage disease, despite treatment with chemotherapy (Foster 2009).

Limited-Stage SCLC

Patients with limited-stage SCLC are treated with a combined modality of chemotherapy and radiation. Investigators compared concurrent chemotherapy and radiation with sequential chemotherapy followed by radiation. Concurrent chemotherapy and radiation improved the median overall survival from 19.7 months to 27.2 months (Takada 2002). Radiation should start with the first or second cycle of chemotherapy.

The chemotherapy regimen should consist of a platinum agent plus etoposide. Most commonly, patients receive cisplatin on day 1 and etoposide on days 1–3. This regimen is repeated every 21 days for a maximum of four to six cycles, depending on response. Carboplatin may be substituted for cisplatin because it is less toxic to the kidneys, but with more myelosuppression. Although the mechanism is not well understood, growth factor support is not recommended in limited-stage SCLC because of the risk of increased pneumonitis with radiation. Thoracic radiation is given concurrently and typically as fractionated doses over 3–7 weeks for a total dose of 45–70 Gy. Ongoing studies are evaluating whether once- or twice-daily radiation most improves survival. Radiation itself improves local disease control by about 25% over chemotherapy alone, but it should be used in combination, whenever possible, to get the most survival benefit (Stinchcombe 2010; Socinski 2007; Bogart 2004; Simon 2004).

Extensive-Stage SCLC

Patients with extensive-stage SCLC are typically not eligible for surgical resection or combined chemotherapy and radiation because of the widespread disease presentation. Treatment options include either a platinum-based and etoposide regimen similar to that in patients with limited-stage SCLC or a combination of cisplatin and irinotecan. The irinotecan and cisplatin regimen consists of cisplatin on day 1 and irinotecan on days 1, 8, and 15. This is repeated every 28 days for four to six cycles. Treatment with either cisplatin or carboplatin is acceptable for extensive-stage SCLC, given that a meta-analysis showed no significant difference in response rate or overall survival between regimens (Rossi 2012).

Although radiation is not used concurrently with chemotherapy for patients with extensive-stage disease, it can be given in the palliative setting. Patients with painful bone metastases or bulky disease may benefit from radiation to have local tumor control and possibly pain relief.

Prophylactic Cranial Irradiation

Almost half of patients with SCLC will develop brain metastases during their disease. For patients with no evidence of brain metastasis, prophylactic cranial irradiation (PCI) may be offered to reduce the incidence of brain metastases in both limited- and extensive-stage SCLC. Prophylactic cranial irradiation therapy consists of 25 Gy of radiation given in 10 daily doses; it should be given after completion of chemotherapy and thoracic radiotherapy. Although studies in the literature are conflicting on the survival impact of PCI, a meta-analysis of over 950 patients showed that patients who had a complete response to systemic therapy were most likely to benefit from PCI. Initial PCI therapy resulted in a 25% decrease in the 3-year incidence of brain metastases as well as a 5.4% improvement in overall survival in patients responding to chemotherapy (Le Pechoux 2009; Slotman 2007). However, patients who receive PCI are at risk of neurotoxicity from the treatment. This can present as subjective cognitive decline or abnormalities on brain imaging and can continue to worsen for years after treatment. The incidence of long-term neurotoxicity from PCI is not well described in the literature due to the difficulty of assessment, but patients who are thought to be at the greatest risk include those with a poor performance status, baseline impaired neurocognitive function, and those who had a complete response to chemotherapy. Patients should be counseled before receiving PCI about the potential benefits and the risk of long-term neurotoxicity from the treatment.

CLASSIFICATION OF NSCLC

Determining the histology of lung cancer as well as the presence of molecular aberrations helps determine therapy. The initial evaluation establishes the origin of the tumor cell by immunohistochemical staining and further classifies it as one of the various types of lung cancer, including small cell carcinoma, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. This information is correlated with the clinical scenario and the radiologic findings to make the diagnosis. If the pathology is consistent with adenocarcinoma, the specimen should undergo further testing to determine whether the patient has any biomarkers that can be used for potential targets for treatment (NCCN 2016).

Biomarkers

Biomarkers are cell characteristics that either have a potential impact on prognosis or indicate potential response to a particular therapy. They can be gene rearrangements, mutations, or genetic traits specific for that disease. Drugs are currently available to target the anaplastic lymphoma kinase (*ALK*) fusion oncogene, epidermal growth factor receptor (*EGFR*) mutations, and ROS proto-oncogene 1 (*ROS1*) gene rearrangements. The presence of a *KRAS* mutation is a predictor of a poorer prognosis and confers resistance to *EGFR*-directed therapy. Although any histology of lung cancer may have *ALK*, *EGFR*, or *ROS1* gene arrangements, it most commonly occurs in the adenocarcinoma histology. Alterations in *ALK*, *EGFR*, *ROS1*, and *KRAS* are typically mutually exclusive (NCCN 2016).

ALK *Fusion Oncogene Rearrangement*

Anaplastic lymphoma kinase rearrangement is a fusion between the *ALK* and *EML4* (echinoderm microtubule-associated protein-like 4) genes that occurs globally in about 2%–7% of patients with NSCLC. Anaplastic lymphoma kinase testing is done by fluorescence in situ hybridization and is required before treatment with any *ALK* inhibitor therapy. In adenocarcinoma, the incidence of *ALK* rearrangements increases to about 30% of patients. Patients with *ALK*-positive disease are often younger, male, and nonsmokers (NCCN 2016).

EGFR *Mutations*

Response to *EGFR*-directed therapy is driven more by *EGFR* mutations than the presence or amplification of the *EGFR* gene. The *EGFR* mutations most commonly occur in adenocarcinoma, but they can occur in other lung cancer histologies as well. Globally, about 15% of patients with lung cancer have an activating *EGFR* mutation, but this varies depending on ethnicity. Although 10% of whites are estimated to have an *EGFR* mutation, up to 50% of Asian patients are *EGFR* mutation positive. An activating mutation confers activation in the tyrosine kinase domain and increased sensitivity to *EGFR* tyrosine kinase inhibitors. The most common activating mutations within *EGFR* are within the exon 19 and 21 domains (exon 19 del and exon 21 [L858R]). Once treated with an *EGFR* inhibitor, patients can acquire further mutations within the *EGFR* domain. The most widely recognized is a T790M mutation, which confers resistance to earlier generations of *EGFR* inhibitors such as gefitinib, erlotinib, and afatinib. Osimertinib, a third-generation *EGFR* inhibitor, has been approved and has activity against the T790M acquired mutation (NCCN 2016).

ROS1 *Gene Rearrangement*

The *ROS1* is a receptor tyrosine kinase within the insulin receptor family, present in about 2% of all lung tumors. This rearrangement results in activation of cellular pathways that increase cell growth and proliferation. Similar to *ALK* rearrangements, *ROS1* rearrangements are most common in nonsmokers or light smokers, those of younger age, and those with an adenocarcinoma histology.

KRAS *Mutations*

A *KRAS* mutation is a poor prognostic biomarker in lung cancer and confers shorter survival. Around 25% of patients with an adenocarcinoma will have a *KRAS* mutation, which is

Table 2-1. Staging of NSCLC

Clinical Stage	Tumor Characteristics	Treatment Category
IA	Tumor ≤ 3 cm with no lymph nodes involved	Resectable
IB	Tumor > 3 cm but ≤ 5 cm with no lymph nodes involved	Resectable
IIA	Tumor > 5 cm, but ≤ 7 cm with no lymph nodes OR Tumor ≤ 7 cm with adjacent lymph nodes positive	Resectable
IIB	Tumor > 5 cm but ≤ 7 cm with adjacent lymph nodes positive OR Tumor > 7 cm or invades local structure with no lymph nodes positive	Resectable
IIIA	Any tumor size with adjacent lymph nodes involved or ipsilateral mediastinal and/or subcarinal lymph nodes OR Tumor invading the mediastinum, heart, esophagus, or trachea and no nodal involvement or adjacent lymph nodes	Resectable or locally advanced unresectable
IIIB	Tumor invading the mediastinum, heart, esophagus, or trachea and nodal involvement in the ipsilateral mediastinal and/or subcarinal OR Any tumor size with nodal involvement in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular	Resectable or locally advanced unresectable
IV	Any tumor size, any nodal involvement, and metastasis to the contralateral lobe, pleural effusions or distant metastasis	Metastatic disease

NSCLC = non–small cell lung cancer.

Information from: Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260-71; and Rami-Porta R, Blejack V, Goldstraw P. The new tumor, node, and metastasis staging system. Semin Respir Crit Care Med 2011;32:44-51.

associated with a smoking history. Having a *KRAS* mutation is predictive of a lack of efficacy with *EGFR* tyrosine kinase inhibitors. Currently, no targeted therapy is available for patients with *KRAS* mutations (NCCN 2016).

Staging of NSCLC

Staging NSCLC helps dictate treatment and prognosis. Patients with localized NSCLC have an overall 5-year survival of 54.8% compared with 4.2% of patients with metastatic disease (Siegel 2016).

Non–small cell lung cancer is staged according to tumor size (T), nodal involvement (N), and distant metastasis (M). This staging system is called the TNM staging system. This classification can then be translated into a clinical staging system that divides patients into stage I–IV. Table 2-1 further describes the clinical staging.

NSCLC TREATMENT OF EARLY-STAGE DISEASE

Early-stage NSCLC is defined as disease that is confined to one lung with minimum involvement of adjacent lymph nodes or clinical stages I and II and resectable stage III. Primary treatment modalities used for early-stage disease are surgery and adjuvant chemotherapy. If a patient is not a candidate or refuses surgery, radiation therapy together with chemotherapy is an alternative. If a patient has a poor performance status (PS) and cannot undergo either surgery or concurrent chemotherapy and radiation, radiation alone may be offered for palliation and symptom management. Performance status is further defined in Table 2-2.

All patients with early-stage NSCLC should be evaluated for surgical resection, given that this has the best chance for a cure and improved overall survival. If a patient has stage III disease that is deemed resectable by a thoracic surgeon, surgery should be pursued. The type of resection needed–a wedge resection, a lobectomy, or a pneumonectomy–depends on the location of the tumor and the pulmonary reserve of the patient. During the surgical procedure, lymph nodes should be tested for any presence of cancer cell spread (NCCN 2016).

After resection, adjuvant chemotherapy with four cycles of a platinum-based regimen may be given to reduce both local and distant recurrences. Table 2-3 describes common adjuvant regimens. Unless there are other patient or

Table 2-2. ECOG Performance Status

Grade	Description
0	Fully active and able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about > 50% of waking hours
3	Capable of only limited self-care, and confined to bed or chair > 50% of waking hours
4	Completely disabled and cannot carry on any self-care activities. Totally confined to bed or chair
5	Dead

Information from: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

Table 2-3. Chemotherapy Regimens for Adjuvant NSCLC

Regimen	Frequency
Cisplatin 50 mg/m^2 on days 1 and 8 Vinorelbine 25 mg/m^2 on days 1, 8, 15, 22	Every 28 days for four cycles
Cisplatin 100 mg/m^2 on day 1 Vinorelbine 30 mg/m^2 on days 1, 8, 15, 22	Every 28 days for four cycles
Cisplatin 100 mg/m^2 on day 1 Etoposide 100 mg/m^2 on days 1–3	Every 28 days for four cycles
Cisplatin 75 mg/m^2 on day 1 Gemcitabine 1250 mg/m^2 on days 1, 8	Every 21 days for four cycles
Cisplatin 75 mg/m^2 on day 1 Docetaxel 75 mg/m^2 on day 1	Every 21 days for four cycles
Cisplatin 75 mg/m^2 on day 1 Pemetrexed 500 mg/m^2 on day 1 **(non-squamous etiologies)**	Every 21 days for four cycles
Paclitaxel 200 mg/m^2 on day 1 Carboplatin AUC 6 on day 1 (for patients who cannot tolerate cisplatin)	Every 21 days for four cycles

Information from: Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97; Arriagada R, Bergman B, Dunat A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60; Douillard J, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomized controlled trial. Lancet Oncol 2006;7:719-27; Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-24; Kreuter M, Vansteenkiste J, Fischer JR, et al. Three-year follow-up of a randomized phase II trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine (the TREAT study). J Thorac Oncol 2016;11:85-93; and Strauss GM, Herndon JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.

disease risk factors, most patients with stage I disease do not receive adjuvant chemotherapy because it has not been shown to improve overall survival in this population. Patients with stage I disease who would potentially benefit from adjuvant chemotherapy include those with positive resection margins, poorly differentiated tumors, vascular invasion, tumors larger than 4 cm, and pleural involvement or if the lymph node sampling was not complete (Butts 2010; Douillard 2006; Winton 2005).

The benefit of adjuvant chemotherapy is clearer in patients with stage II and III disease, according to a subgroup of the Adjuvant Navelbine International Trialist Association (ANITA) trial. In the ANITA trial, patients with stage II and III who received four cycles of cisplatin and vinorelbine after surgery had an 8.6% improvement in 5-year overall survival over placebo (Douillard 2006). The Lung Adjuvant Cisplatin Evaluation meta-analysis combined five large adjuvant trials, which included cisplatin plus vinorelbine, cisplatin plus etoposide, or cisplatin plus docetaxel regimens, and found that adjuvant therapy with a cisplatin-based regimen resulted in a statistically significant survival benefit of 5.4% over no adjuvant chemotherapy at 5 years. There was no statistical difference in outcomes when comparing any of the cisplatin-based regimens (Pignon 2008). Table 2-3 further describes the treatment options available for adjuvant therapy.

Carboplatin may be substituted for cisplatin in patients who cannot tolerate cisplatin, such as an older patient or someone with renal impairment, especially if a patient's CrCl is less than 60 mL/minute/1.73 m^2. The Cancer and Leukemia Group B 9633 trial randomized 344 patients with stage IB NSCLC to either paclitaxel and carboplatin adjuvant therapy or observation. This trial showed a 3-year improved overall survival of 7%, but it did not maintain significance after 6 years. The authors concluded that carboplatin and paclitaxel was an alternative for patients who cannot tolerate a cisplatin-based regimen; however, the trial was underpowered to show a true difference in overall survival in patients with stage IB disease (Strauss 2008).

The role of molecular biomarkers in the adjuvant setting and early-stage NSCLC is not yet defined. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials is evaluating the benefit of *EGFR*- or *ALK*-targeted therapy compared with placebo in patients with activating mutations or gene rearrangements.

NSCLC TREATMENT OF UNRESECTABLE OR LOCALLY ADVANCED STAGE III

In unresectable or locally advanced-stage III NSCLC, neoadjuvant therapy may be given to shrink the tumor if the patient is deemed a surgical candidate. However, not all patients with unresectable stage III disease are candidates for or will benefit from neoadjuvant therapy and undergo concurrent chemoradiation. Although the treatment goal for locally advanced stage III NSCLC is still cure, the overall 5-year survival remains around 30%, despite optimal therapy with chemotherapy, radiation, and potentially surgical resection.

Table 2-4 defines the most common regimens used in combination with radiation. There are no trials comparing one regimen to the other, so all are considered suitable options for patients with stage III locally advanced or unresectable disease. Ideally, the chemotherapy should begin with the first or second day of radiation.

Typically, patients receive a total of 60–70 Gy of radiation over 6–7 weeks. This can be given in daily or twice-daily doses. Patients receiving twice-daily doses have improved overall survival and disease-free survival, but they have increased toxicity over patients receiving once-daily radiation. Therefore, the patients selected for twice-daily radiation must have a good PS and otherwise be healthy (NCCN 2016).

NSCLC TREATMENT OF RECURRENT OR METASTATIC DISEASE

If a patient has recurrent disease or has metastatic disease at presentation, the goal of therapy shifts from a curative to a palliative intent, meaning the aim of the treatment is to prevent the cancer from spreading. The main modality of treatment is chemotherapy. Radiation is typically reserved for palliation of patients with pain or shortness of breath.

With the advent of targeted therapy, all patients with metastatic disease should have their tumor tested for molecular aberrations such as *EGFR* mutations, *ALK* rearrangements, *ROS1*, and *KRAS* at diagnosis. If a patient has a targetable mutation such as *EGFR*, *ALK*, or *ROS1*, therapy directed at that target should be given before chemotherapy.

If a patient has a PS of 3 or 4, best supportive care is recommended instead of chemotherapy. For patients with a good PS (PS 0–2) and without any activating mutations, combination chemotherapy is recommended as a first-line treatment. This usually consists of carboplatin or cisplatin plus a chemotherapy of another class, such as paclitaxel, pemetrexed in non-squamous histologies, or gemcitabine for four to six cycles of treatment.

A phase III trial was completed with 1155 patients with advanced-stage NSCLC randomized to three different cisplatin-based arms or one carboplatin-based arm. The overall response rate and overall survival did not differ between the groups, indicating that the chemotherapy regimen should be chosen according to the adverse effect profile of the drugs and patient comorbidities (Schiller 2002). Many clinicians use a carboplatin-based regimen in the metastatic setting because of the improved tolerability over cisplatin-based regimens, especially in the older population. Patients typically receive four to six cycles of the combination chemotherapy, after which they are assessed for maintenance treatment according to histology.

Table 2-4. Chemotherapy Regimens for Concurrent Chemoradiation for NSCLC

Chemotherapy Regimen	Frequency
Cisplatin 50 mg/m^2 on days 1, 8, 29, 36 Etoposide 50 mg/m^2 on days 1–5, 29–33	Concurrent radiation administered daily
Carboplatin AUC 5 on day 1 Pemetrexed 500 mg/m^2 on day 1 **(non-squamous histologies)**	Every 21 days for four cycles with concurrent radiation
Cisplatin 75 mg/m^2 on day 1 Pemetrexed 500 mg/m^2 on day 1 **(non-squamous histologies)**	Every 21 days for three cycles with concurrent radiation
Cisplatin 100 mg/m^2 on days 1 and 29 Vinblastine 5 mg/m^2 weekly for 5 wk	Concurrent radiation administered daily
Paclitaxel 45–50 mg/m^2 weekly Carboplatin AUC 2 weekly → Paclitaxel 200 mg/m^2 on day 1 Carboplatin AUC 6 on day 1	Weekly paclitaxel/carboplatin while receiving thoracic radiation, followed by two cycles of consolidation with paclitaxel/carboplatin every 3 wk

Information from: Albain KS, Crowley JJ, Turrisi AT, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 2002;20:3454-60; Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120-5; Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. Lung Cancer 2015;87:232-40; Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011;103:1452-60; Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multimodality protocol. J Clin Oncol 2005;23:5883-91.

Adenocarcinoma and Large Cell Carcinoma

In a phase III trial, investigators randomized 1725 patients with metastatic NSCLC to either cisplatin and gemcitabine or cisplatin and pemetrexed. Although the median overall survival for the trial did not differ between groups, a prespecified subset analysis according to histology showed that patients with adenocarcinoma randomized to cisplatin and pemetrexed had a statically significant improvement in median overall survival over cisplatin and gemcitabine (12.6 vs. 10.9 months, p=0.03). Patients with a squamous cell histology, however, had a lower median overall survival with cisplatin and pemetrexed compared with cisplatin and gemcitabine (9.4 months vs. 10.8 months, HR 1.23; p=0.05). Because of the lower overall survival, pemetrexed-based regimens are not recommended for patients with squamous histologies (Scagliotti 2008).

The role of pemetrexed was further explored in a randomized clinical trial including patients with a lower PS of 2 and NSCLC. Patients were randomized to either pemetrexed single agent or pemetrexed and carboplatin combination therapy for four cycles. All patients received supplementation with folic acid daily and vitamin B_{12} to reduce the incidence of hematologic adverse events from pemetrexed therapy. The median overall survival for pemetrexed alone was 5.3 months compared with 9.3 months for the combination group (p=0.001), indicating that even for patients with a PS of 2, combination chemotherapy should be pursued (Zukin 2013). Although there is no head-to-head trial of cisplatin and pemetrexed compared with carboplatin and pemetrexed, these regimens are commonly thought to perform similarly with respect to clinical outcomes, and carboplatin is associated with fewer adverse events.

The optimal number of chemotherapy cycles required in metastatic NSCLC is debatable. Continuing beyond four to six cycles of platinum-based chemotherapy does not improve overall survival but does increase toxicity. The PARAMOUNT trial looked at the impact of pemetrexed continuation maintenance therapy immediately after initial therapy with cisplatin and pemetrexed. Only patients with no disease progression were continued on either pemetrexed every 3 weeks or best supportive care. The pemetrexed continuation maintenance group had an overall survival of 13.9 months compared with best supportive care at 11 months (p=0.0195) (Paz-Ares 2013). Pemetrexed continuation maintenance therapy is now

the standard of care for patients who have no disease progression on initial platinum/pemetrexed therapy for non–squamous cell lung cancer. Patients continue therapy until disease progression or intolerability. Patients who received a different platinum-doublet therapy such as carboplatin and paclitaxel initially may still benefit from pemetrexed continuation therapy. Changing to pemetrexed is called "switch maintenance therapy" because the patient is changing chemotherapy regimens. If patients had no disease progression after their platinum-based regimen, they would be changed to pemetrexed maintenance therapy until disease progression or intolerability (Gerber 2013). Other options for continuing maintenance therapy are with gemcitabine or switch maintenance therapy for erlotinib, but these strategies are not as commonly used in practice (NCCN 2016).

One target of cancer treatment is to reduce the ability of the cancer cell to form new blood vessels or angiogenesis. Because adenocarcinoma tends to occur in the periphery of the lung, it is less likely to cause bleeding than more centrally located tumors such as squamous cell cancer or SCLC. Use of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab has been explored in the first-line setting in combination with a paclitaxel/platinum regimen and a pemetrexed/platinum regimen in patients with a good PS of 0–1.

Because of the risk of bleeding and thrombosis from VEGF inhibition, patients must be carefully screened before starting therapy with bevacizumab. If a patient has had recent hemoptysis, serious bleeding, or recent major surgery, bevacizumab is contraindicated. Caution should be used in patients with untreated brain metastases, uncontrolled hypertension, proteinuria, or new clots. A phase III randomized trial comparing carboplatin and paclitaxel with carboplatin, paclitaxel, and bevacizumab showed a statistically significant improved overall survival of 12.3 months in the bevacizumab group versus 10.3 months in the chemotherapy-only group (p=0.0003). Of note, there were 15 treatment-related deaths in the bevacizumab group, including five pulmonary hemorrhages (Sandler 2006).

The AVAPERL trial evaluated maintenance therapy with both bevacizumab and pemetrexed in patients who received cisplatin, pemetrexed, and bevacizumab initially. Patients were randomized to receive either maintenance therapy with bevacizumab and pemetrexed or bevacizumab maintenance therapy alone. Maintenance therapy with bevacizumab and pemetrexed resulted in a 3.7-month increase in progression-free survival (p<0.001) but no effect on overall survival, indicating that continuation maintenance with pemetrexed and bevacizumab is a feasible option if the patient is tolerating therapy (Barlesi 2014). Because of this trial, bevacizumab gained FDA label approval for the treatment of metastatic non–squamous cell lung cancer and has been used in combination therapy with a platinum plus paclitaxel or pemetrexed regimen first line and as a single agent in maintenance therapy.

Squamous Cell Carcinoma

Except for platinum and pemetrexed regimens, several platinum-based doublets are effective for the treatment of squamous cell carcinoma. In general, the progression-free and overall survival benefits in squamous cell carcinoma are not as robust as in adenocarcinoma. Squamous cell NSCLC has a low incidence of having an activating mutation within *EGFR* or an *ALK* oncogene rearrangement. Chemotherapy for squamous cell histology is usually a platinum agent combined with paclitaxel or gemcitabine.

Weekly albumin-bound paclitaxel has been studied in combination with carboplatin and compared with carboplatin and conventional paclitaxel in patients with advanced or metastatic NSCLC. All histologies were included, but patients with squamous cell lung cancer had the most benefit, with a 41% overall response rate with albumin-bound paclitaxel compared with a 26% overall response rate with conventional paclitaxel (95% CI, 1.271–2.221; p<0.001). However, there was no statistically significant improvement in progression-free survival (p=0.214) or median overall survival (12.1 months for carboplatin and albumin-bound paclitaxel compared with 11.2 months for carboplatin and paclitaxel, p=0.271) (Socinski 2012).

The SQUIRE trial evaluated whether adding a monoclonal *EGFR* inhibitor necitumumab to cisplatin and gemcitabine would improve overall survival compared with cisplatin and gemcitabine alone; *EGFR*-activating mutations or overexpression did not have to be present for the trial. Necitumumab was given on days 1 and 8 of each of the four cycles of cisplatin and gemcitabine, followed by continuation maintenance therapy with necitumumab. The addition of necitumumab produced statistically significant improvement in overall survival (11.5 months) compared with cisplatin and gemcitabine alone (9.9 months; p=0.01). However, adding necitumumab increased *EGFR*-related toxicity such as acne-like rash, hypomagnesemia, and infusion-related reactions (Thatcher 2015). With the modest improvement in overall survival, increased toxicity and cost, the National Comprehensive Cancer Network (NCCN) has removed this regimen from its most recent guidelines (NCCN 2016).

Although not studied in the SQUIRE trial, some patients who respond to first-line cisplatin and gemcitabine may receive continuation maintenance therapy with gemcitabine alone. In addition, switch maintenance therapy to docetaxel is an option for patients who respond to the initial chemotherapy treatment (NCCN 2016). Table 2-5 describes the most commonly used first-line combination regimens for metastatic disease by histology.

EGFR Mutation–Positive Disease

The *EGFR* mutations are more commonly associated with nonsmokers, females, and patients of Asian descent. All patients with adenocarcinoma should be tested for the presence of activating mutations. Options for these patients include

Table 2-5. Most Commonly Used First-line Chemotherapy Regimens for Metastatic NSCLC by Histology

Chemotherapy Regimen	Continuation Maintenance Therapy
Adenocarcinoma, Large Cell	
Carboplatin AUC 5 on day 1 Pemetrexed 500 mg/m^2 on day 1 Every 21 days for 4 cycles	Pemetrexed 500 mg/m^2 every 21 days until disease progression
Cisplatin 75 mg/m^2 on day 1 Pemetrexed 500 mg/m^2 on day 1 Every 21 days for 6 cycles	Pemetrexed 500 mg/m^2 every 21 days until disease progression
Carboplatin AUC 6 on day 1 Pemetrexed 500 mg/m^2 on day 1 Bevacizumab 15 mg/kg on day 1 Every 21 days for 6 cycles	Pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg every 21 days until disease progression
Cisplatin 75 mg/m^2 on day 1 Pemetrexed 500 mg/m^2 on day 1 Bevacizumab 7.5 mg/kg on day 1 Every 21 days for 4 cycles	Pemetrexed 500 mg/m^2 and bevacizumab 7.5 mg/kg every 21 days until disease progression
Carboplatin AUC 6 on day 1 Paclitaxel 225 mg/m^2 on day 1 Every 21 days for 6 cycles	For adenocarcinoma, consider changing therapy to maintenance pemetrexed 500 mg/m^2 every 21 days until disease progression
Carboplatin AUC 6 on day 1 Paclitaxel 200 mg/m^2 on day 1 Bevacizumab 15 mg/kg on day 1 Every 21 days for 6 cycles	Bevacizumab 15 mg/kg every 21 days until disease progression For adenocarcinoma, consider changing therapy and adding maintenance pemetrexed 500 mg/m^2 every 21 days until disease progression
Squamous Cell	
Carboplatin AUC 6 on day 1 Paclitaxel 225 mg/m^2 on day 1 Every 21 days for 6 cycles	
Carboplatin AUC 6 on day 1 Albumin-bound paclitaxel 100 mg/m^2 on days 1, 8, 15 Every 21 days for 6 cycles	
Cisplatin 80 mg/m^2 on day 1 Gemcitabine 1000 mg/m^2 on days 1, 8 Every 21 days for 6 cycles	Can consider gemcitabine continuation maintenance therapy for patients responding to therapy

Information from: Zukin M, Barrios, CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. J Clin Oncol 2013;31:2849-53; Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51; Patel JD, Hesing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-9; Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small-cell lung cancer: AVAPERL (MO22089). J Clin Oncol 2013;31:3004-11; Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-8; Sandler A, Gray R, Perry M, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer N Engl J Med 2006;355:2542-50; Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial J Clin Oncol 2012;30:2055-62.

small molecule oral tyrosine kinase inhibitors such as erlotinib, gefitinib, and afatinib or chemotherapy for the treatment of their disease. If the mutation status is unknown and treatment is urgent, chemotherapy may be initiated but changed if a mutation is discovered.

Therapy should be started with a tyrosine kinase *EGFR* inhibitor in the first-line setting if an *EGFR*-activating mutation is known. Erlotinib, gefitinib, and afatinib are all approved as first-line therapy, but erlotinib is the most commonly used because of its widespread availability and overall tolerability. Erlotinib 150 mg orally daily was evaluated in the first-line setting in the EURTAC trial, in which patients were randomized to receive continuous oral dosing of erlotinib or conventional chemotherapy. Median progression-free survival was 9.7 months with erlotinib compared with 5.2 months with chemotherapy ($p<0.0001$). Erlotinib was better tolerated than chemotherapy, but it resulted in an increase in *EGFR*-associated rash in 13% of patients with a grade 3 or 4 rash (Rosell 2012).

Gefitinib was recently reapproved by the FDA because of a phase IV clinical trial that showed a median progression-free survival of 9.7 months and overall survival of 19.2 months in patients who received gefitinib 250 mg orally daily in the first-line setting (Douillard 2014). This confirmed an earlier phase III trial in which patients receiving gefitinib had improved progression-free survival and response rate over initial chemotherapy but not overall survival. The lack of improvement in overall survival was thought to have been a result of the crossover effect (Fukuoka 2011).

The LUX-Lung trials evaluated afatinib in a variety of settings for *EGFR* mutation–positive disease. Afatinib differs from erlotinib and gefitinib because it is an irreversible inhibitor of *EGFR*. Having an irreversible inhibitor of *EGFR* is thought to increase the efficacy of the drug as well as increase adverse effects such as diarrhea. The LUX-Lung 3 trial compared afatinib 40 mg orally daily with cisplatin and gemcitabine chemotherapy. Afatinib showed improved progression-free survival (11.1 months vs. 6.9 months). Adverse effects with afatinib were diarrhea (100%), rash (91.9%), and stomatitis (85.5%). Twenty-nine percent of patients discontinued afatinib because of adverse events (Sequist 2013).

ALK-Positive Disease

Patients who test positive for *ALK* rearrangements should receive *ALK*-directed therapy before conventional chemotherapy. The *ALK* inhibitors currently on the market are crizotinib, ceritinib, and alectinib. Crizotinib is the only *ALK* inhibitor that gained FDA approval for first-line therapy in the metastatic setting. Approval was based on a phase III trial that compared crizotinib therapy with traditional chemotherapy in patients with *ALK* rearrangement in which patients received either crizotinib 250 mg orally twice a day or chemotherapy with platinum and pemetrexed. The median progression-free survival was significantly longer in the crizotinib arm than in the chemotherapy group (10.9 months vs. 7.0 months, $p<0.0001$). Crizotinib was well tolerated, except for visual disturbances (71%) and diarrhea (61%) (Solomon 2014).

ROS1 Gene Rearrangement Disease

The *ROS1* gene is related to the *ALK* gene family, and rearrangement occurs in about 1% of patients with lung cancer. The kinase domains of *ALK* and *ROS1* are similar and share 77% of amino acid identity. A phase I trial of 50 patients with *ROS1* rearrangement–positive disease were treated with crizotinib 250 mg twice daily. The overall response rate was 72%, with a median progression-free survival of 19.2 months. This was the first trial to show that an *ALK* inhibitor also inhibits *ROS1* (Shaw 2014a).

Programmed Death-Ligand 1 Expressive Disease

One of the known mechanisms by which cancer cells escape cell death is the result of down-regulation of the immune system. Activated T cells express programmed cell death protein 1 receptors (PD-1), which bind to ligands such as programmed death-ligand 1 (PD-L1), which are expressed on cancer cells. This interaction leads to the immune system not attacking cancer cells. Immune checkpoint inhibitors inhibit the binding of PD-1 to PD-L1, resulting in an increase in activated T cells to attack the tumor. Although the role of PD-1 and PD-L1 inhibitors has been established in the second-line setting, their role in initial therapy was only recently explored. In the second-line setting, patients whose tumors have a higher expression of PD-L1 have a longer survival receiving immunotherapy than patients whose tumors do not express PD-L1.

The KEYNOTE-024 trial was a randomized, phase III international study that randomized 305 patients with newly diagnosed metastatic NSCLC to receive either pembrolizumab, a PD-1 inhibitor, 200 mg intravenously every 3 weeks for 35 cycles or the investigators' choice of platinum-based chemotherapy for four to six cycles: carboplatin and pemetrexed, cisplatin and pemetrexed, carboplatin and gemcitabine, cisplatin and gemcitabine, or carboplatin and paclitaxel. Patients who received chemotherapy with pemetrexed could receive pemetrexed maintenance therapy after completing the four to six cycles. Patients must have had a tumor that had at least a 50% expression of PD-L1. The median progression-free survival was 10.3 months for pembrolizumab and 6 months for the chemotherapy arm ($p<0.001$). Given the positive results of the KEYNOTE-024 trial, pembrolizumab recently gained FDA approval for front-line treatment of NSCLC in patients with no EGFR mutation or ALK rearrangement and tumors expressing at least 50% PD-L1 (Reck 2016).

Patient Care Scenario

L.R. is a 67-year-old Asian woman who presents to the clinic with newly diagnosed adenocarcinoma of the lung metastatic to the liver and bone. Her medical history is significant for diabetes and COPD.

Her current medications include metformin 500 mg by mouth twice daily, glipizide 5 mg by mouth twice daily, and tiotropium 18 mcg inhaled daily. Baseline laboratory values include SCr 1.2 mg/dL, bilirubin 0.8 mg/dL, Hgb 9.7 g/dL, Plt 178,000/mm^3, and WBC 7.8 x 10^3 cells/mm^3.

You are asked to determine the most appropriate treatment approach for L.R.

ANSWER

Clinical stage should be determined first. With the presence of metastatic disease, she has clinical stage IV disease. This means that treatment options should focus on chemotherapy, targeted therapy or immunotherapy, not surgery or radiation. The patient has three characteristics that increase her chance of having an activating *EGFR* mutation or *ALK* rearrangement: Asian, female, and adenocarcinoma. Even with the known characteristics, it is recommended that biomarker testing be done before starting therapy.

If the patient has an activating *EGFR* mutation, therapy with a tyrosine kinase *EGFR* inhibitor should be initiated first line. Erlotinib is usually initiated because of its tolerability and because it improves progression-free and overall survival over doublet chemotherapy, according to the results of the EURTAC trial. Gefitinib and afatinib are also feasible options, but afatinib is typically not used as first-line treatment because it has a higher incidence of the adverse events of diarrhea and rash over erlotinib.

If the patient does not have an activating *EGFR* mutation or *ALK* rearrangement, the pathology should be tested for PD-L1 expression. If the tumor has > 50% expression of PD-L1, then initiation of pembrolizumab as first-line therapy would be appropriate.

If the patient does not have an activating mutation or >50% expression of PD-L1, she should be initiated on a chemotherapy doublet regimen with a platinum backbone and pemetrexed. The patient's bleeding and thrombosis risk should be assessed before initiating concurrent bevacizumab.

1. Barlesi F, Scherpereel A, Gorbunova V, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol 2014;25:1044-52.
2. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small cell lung cancer. N Engl J Med 2016;375:1823-33.
4. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-51.

NSCLC METASTATIC DISEASE SECOND-LINE THERAPY

Despite treatment, metastatic NSCLC often progresses and requires subsequent therapy. The principles of treatment are the same with second-line therapy as with initial therapy: if a patient has a mutation or a genetic alteration, targeted therapy is preferable to chemotherapy. Traditionally, docetaxel chemotherapy has been the standard of care for all NSCLC histologies. This was based on a trial comparing docetaxel every 3 weeks with best supportive care, in which docetaxel improved overall survival by 2.4 months (p=0.047) (Shepherd 2000). Since then, researchers have explored the use of other targeted agents and immunotherapy in this setting.

VEGF Targeted Therapy

A second VEGF inhibitor, ramucirumab, gained FDA approval for second-line therapy for patients with NSCLC. Ramucirumab binds specifically to VEGF receptor 2 (VEGFR2) and blocks the binding of VEGF receptor ligands. The REVEL trial assessed patients after disease progression on first-line chemotherapy with either ramucirumab and docetaxel or docetaxel alone. Combination therapy resulted in improved overall survival (10.5 months vs. 9.1 months, p<0.023). Patients receiving therapy with ramucirumab had more severe hemorrhage (29%), GI bleeding (3%), and hypertension (11%) (Garon 2014). The adverse event profile of ramucirumab has limited its use in clinical practice because many patients have comorbidities that place them at higher risk of not tolerating ramucirumab.

EGFR-Targeted Therapy

Subsequent therapy for patients with *EGFR*-mutated NSCLC depends on the patient's PS and symptoms. If the patient is asymptomatic, continuing the current *EGFR* inhibitor may be considered (NCCN 2016). If the patient has symptoms or rapid disease progression, options include changing to immunotherapy, chemotherapy, or another *EGFR* inhibitor such as afatinib. Use of afatinib in the second-line setting is

being debated because of the results of the LUX-Lung 1 trial, a phase IIb/III trial, in which the median overall survival after disease progression on *EGFR* therapy was no better with afatinib than with placebo (10.8 months afatinib vs. 12 months placebo, p=0.74). Progression-free survival was improved with afatinib at 3.3 months compared with 1.1 months with placebo (p<0.0001) (Miller 2012).

Patients receiving *EGFR*-directed therapy may acquire a T790M mutation, which confers resistance to gefitinib, erlotinib, and afatinib and can occur in up to 60% of patients with progressive disease after initial response to an *EGFR* inhibitor. Osimertinib is a third-generation oral tyrosine kinase inhibitor that inhibits both activating *EGFR* mutations and the T790M mutation. The AURA trial showed a response rate of 61% in patients taking osimertinib after disease progression on *EGFR* inhibitors and a disease control rate of up to 90%. For patients without the T790M mutation, osimertinib was associated with a 21% response rate and a 61% disease control rate. The most common adverse effects with osimertinib are diarrhea (41%), rash (37%), nausea (18%), and dry skin (40%) (Janne 2015).

ALK Inhibitor Therapy

Both ceritinib and alectinib are FDA approved for the treatment of *ALK*-positive metastatic NSCLC after disease progression or intolerance to crizotinib. Ceritinib is dosed at 750 mg orally daily and has efficacy in patients known to be resistant to crizotinib. A phase I trial showed a 56% response rate to ceritinib after disease progression on crizotinib, including responses in patients with CNS metastases (Shaw 2014b). Likewise, alectinib is an oral *ALK* inhibitor that is given orally 600 mg twice daily. In a phase II trial alectinib demonstrated an overall response rate of 48% in patients who had already progressed on crizotinib therapy, including 23 of 84 patients with CNS metastases having a complete response and an overall CNS disease control of 83% (Ou 2016).

The optimal order of *ALK* inhibitors has yet to be determined, but treatment with an *ALK* inhibitor is recommended for the first- and second-line setting before using conventional chemotherapy.

Immunotherapy

The initial role of immunotherapy in NSCLC was in the second-line setting after disease progression on a platinum-based regimen. Immune checkpoint inhibitors inhibit the binding of PD-1 to PD-L1, resulting in an increase in activated T cells to attack the tumor. Inhibition of PD-1 or PD-L1 activates the T cells and may lead to autoimmune conditions such as colitis, hepatitis, pneumonitis, and endocrinopathies. Both nivolumab and pembrolizumab are PD-1 inhibitors and are approved for treatment of NSCLC after disease progression (Herbst 2016; Borghaei 2015; Brahmer 2015). Recently, the first PD-L1 inhibitor, atezolizumab, was approved for the treatment of NSCLC after disease progression, adding another treatment option for these patients (Fehrenbacher 2016). Treatment with PD-1 or PD-L1 inhibitors is associated with immune-related adverse events (IRAEs) and can occur in up to 40% of patients with up to 10% being severe, typically within 3–6 months of initiating treatment. Although most IRAEs are mild and can be symptomatically treated, more severe IRAEs need to be treated with systemic corticosteroids and withholding of the PD-1 or PD-L1 inhibitor. Patients with active autoimmune diseases should be excluded from treatment with immunotherapy due to the increase risk of IRAEs.

Nivolumab

Nivolumab has been evaluated in both squamous cell and non–squamous cell lung cancer after disease progression on a platinum doublet. The CheckMate 017 trial randomized patients with squamous cell lung cancer to nivolumab 3 mg/kg every 2 weeks or docetaxel every 3 weeks. Patients receiving nivolumab had a 9.2-month median overall survival compared with a 6.0-month median overall survival for patients receiving docetaxel (p<0.001), resulting in an HR for death of 0.59. The 1-year overall survival was 42% for nivolumab and 24% for docetaxel. When PD-L1 tumor expression was examined, PD-L1 expression was neither prognostic nor predictive for benefit in squamous cell lung cancer, indicating that PD-L1 expression was not imperative before a treatment decision (Brahmer 2015).

The CheckMate 057 trial was conducted in patients with non–squamous cell lung cancer. This trial randomized patients with non–squamous cell lung cancer in the second-line setting to either nivolumab 3 mg/kg every 2 weeks or docetaxel every 3 weeks. It resulted in a median overall survival of 12.2 months in the nivolumab group and 9.4 months in the docetaxel group, which was statistically significant (p=0.002). The 1-year overall survival was 51% for nivolumab and 39% for docetaxel. Unlike in the CheckMate 017 squamous cell trial, PD-L1 expression in non–squamous cell lung cancer was correlated with improved overall as well as progression-free survival with nivolumab. Although PD-L1 tumor expression was not required for entry into the trial, 78% of patients had quantifiable PD-L1 expression. Expression of PD-L1 was defined as 1% of tumor cells or higher, 5% or higher, and 10% or higher in a section that included at least 100 tumor cells. The higher the percentage of PD-L1 expression, the higher the overall and progression-free survival. Despite this finding, nivolumab can be used in both squamous cell and non–squamous cell histologies without testing for PD-L1 expression (Borghaei 2015). Recently, the FDA changed the dosing recommendation for nivolumab in NSCLC to a flat dosing of 240 mg every 3 weeks instead of the weight-based dosing based on a pharmacokinetic analysis and an evaluation of treatment response relative to exposure.

Pembrolizumab

Pembrolizumab is also a PD-1 inhibitor approved for the treatment of NSCLC after disease progression on chemotherapy. The KEYNOTE-010 trial was a phase II/III study that randomized 1034 patients to pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel every 3 weeks. Patients had to have at least 1% of their tumor cells stained positive for PD-L1 before enrolling in the trial. Overall survival was 10.4 months with pembrolizumab 2 mg/kg (p=0.0008), 12.7 months with pembrolizumab 10 mg/kg (p<0.0001), compared to 8.5 months with docetaxel. Progression-free survival was not statistically different between the groups. In patients with more than 50% PD-L1 expression on the tumor cells, overall survival was increased to 14.9 months with pembrolizumab 2 mg/kg (p=0.008) and 17.3 months for pembrolizumab 10 mg/kg (p<0.001) compared with docetaxel at 8.2 months (Herbst 2016).

Similarly to nivoumab, pembrolizumab is now FDA approved at a flat dosage of 200 mg instead of weight-based dosing, every 3 weeks until disease progression, but the patient must have at least 1% PD-L1 expression on the tumor. An FDA-approved companion diagnostic biomarker test is to be used to determine eligibility for pembrolizumab treatment.

Atezolizumab

Atezolizumab is the first approved PD-L1 inhibitor and is designed to block the PD-L1 while leaving other programmed death ligands available for function, specifically PD-L2, which may in turn result in more immune homeostasis and fewer IRAEs.

The POPLAR trial was a phase II, open-label study that randomized 287 patients with metastatic or recurrent NSCLC who had progressed on platinum-based therapy to either atezolizumab 1200 mg intravenously every 3 weeks or docetaxel therapy. Median overall survival was improved in patients receiving atezolizumab over docetaxel therapy regardless of PD-L1 tumor expression (12.6 months vs. 9.7 months, HR 0.73, p=0.04). Patients with tumors having higher tumor expression of PD-L1 had a longer median overall survival of 15.5 months. The rate of IRAEs was low at less than 5%, suggesting that the PD-L1 inhibitor may have fewer autoimmune complications than the PD-1 inhibitors (Fehrenbacher 2016). A recent phase III trial, the OAK study, was completed and is expected to further define the benefit of atezolizumab in patients with high tumor expression of PD-L1.

FUTURE DIRECTIONS

Dramatic changes have occurred in the past 5 years for the treatment of NSCLC. There is now a greater understanding of the tumor biology with the discovery of mutations, gene rearrangements, and how to use a patient's immune system to fight lung cancer. Now that several modalities are available for the treatment of NSCLC, it is prudent to determine the appropriate order of therapy. We know that for patients with the *EGFR* mutation, EGFR inhibitor therapy should be first-line therapy; however, once disease progression occurs, the role of chemotherapy, additional EGFR inhibition, or immunotherapy is unclear. Moreover, we now have many *EGFR* inhibitors, *ALK* inhibitors, and immunotherapy agents available for use but little information regarding which agent is superior to another or which agent to use first. Although immunotherapy has shown a benefit in the second-line setting for NSCLC, some populations respond better than others. Ongoing clinical trials are determining which patient populations should be treated with immunotherapy and whether this therapy can be combined with chemotherapy to produce better outcomes.

Although NSCLC treatment has changed drastically over the past 5 years, advances in the treatment of SCLC have been minimal. The treatment regimen for SCLC is the same as it has been for the past 30 years. Treatment modalities such as immunotherapy and vaccine therapy are currently being explored in SCLC to determine whether a more sustainable treatment response can be obtained.

Practice Points

- **The decrease in smoking has reduced the incidence of squamous cell lung cancer. However, the incidence of adenocarcinoma lung cancer continues to increase.**
- **Treatment of limited-stage SCLC is combination chemotherapy with cisplatin, etoposide, and radiation therapy.**
- **Surgery is the treatment mainstay of early-stage NSCLC.**
- **Adjuvant chemotherapy with a platinum-based regimen is necessary to reduce local and distant recurrence after resection for stage II and III disease.**
- **If the disease is localized but unresectable, chemotherapy and radiation are the treatment mainstays.**
- ***EGFR*, *ALK*, and *ROS1* mutation analysis is important for patients with metastatic disease, especially with adenocarcinoma.**
- **Pemetrexed-based regimens should only be used in non–squamous cell lung cancer histologies.**
- **Patients should be evaluated for bleeding and thrombosis risk before receiving a VEGF inhibitor such as bevacizumab.**
- **PD-1 inhibitors improve overall survival in all histologies of metastatic NSCLC.**
- **Treatment with pembrolizumab requires at least 1% PD-L1 tumor expression.**

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Self-Assessment Questions

21. A 32-year-old man with no significant medical history presents to his primary care provider with a 3-month history of a nonproductive cough. The patient is a nonsmoker and a social drinker. Imaging reveals a peripheral-based lung mass that is 4.3 x 3.2 cm with no lymph node involvement. Which one of the following is the most likely histology of this patient's presumed lung cancer?

    A. Small cell lung cancer (SCLC)
    B. Adenocarcinoma
    C. Squamous cell lung cancer
    D. Large cell lung cancer

22. A 45-year-old man has newly diagnosed extensive-stage SCLC. His medical history includes diet-controlled diabetes and hypertension. He has a 60 pack-year history of smoking and still smokes ½ pack/day. His family history is positive for a mother with breast cancer and a father with non–small cell lung cancer (NSCLC). Which one of the following risk factors most likely had the greatest effect on this patient's development of SCLC?

    A. Diabetes
    B. Family history
    C. Smoking
    D. Age

23. A 64-year-old woman has newly diagnosed limited-stage SCLC. Her medical history is significant for asthma and hypertension. Pertinent laboratory values include SCr 0.78 mg/dL, K 4.2 mmol/L, bilirubin 0.4 mg/dL, AST 25 IU/L, and ALT 32 IU/L. Which one of the following treatment strategies is best to recommend for this patient?

    A. Cisplatin plus etoposide plus radiation
    B. Carboplatin plus etoposide plus radiation
    C. Cisplatin plus etoposide
    D. Carboplatin plus etoposide

24. A 62-year-old woman with extensive-stage SCLC has completed four cycles of chemotherapy and has had a complete remission. Which one of the following treatment strategies is best to recommend for this patient?

    A. Continue her current chemotherapy regimen for two more cycles.
    B. Offer PCI (prophylactic cranial radiation).
    C. Change to observational status with repeat scans in 3 months.
    D. Change her chemotherapy regimen to cisplatin and irinotecan.

25. A 42-year-old woman has newly diagnosed stage IV NSCLC. Molecular testing showed an *ALK* rearrangement. Which one of the following is the most likely histology of this patient's NSCLC?

    A. SCLC
    B. Adenocarcinoma
    C. Squamous cell carcinoma
    D. Large cell carcinoma

26. A 52-year-old man with stage IV adenocarcinoma receives erlotinib therapy. Which one of the following best describes the most likely mutation or gene alteration in this patient?

    A. T790M
    B. *KRAS*
    C. *ROS1*
    D. Exon 19 del

27. Which one of the following is the most appropriate adjuvant treatment regimen after surgical resection for a 72-year-old patient with a CrCl of 30 mL/minute/1.73 m^2 and stage II adenocarcinoma NSCLC?

    A. Radiation to the surgical bed
    B. Cisplatin and vinorelbine for four cycles
    C. Cisplatin and pemetrexed for four cycles
    D. Carboplatin and paclitaxel for four cycles

28. A 65-year-old man has a newly diagnosed stage III nonresectable NSCLC invading the esophagus. His medical history is significant for rheumatoid arthritis, diabetes, and chronic kidney disease. Which one of the following is the best treatment strategy to recommend for this patient?

    A. Concurrent chemotherapy and radiation
    B. Radiation followed by chemotherapy
    C. Neoadjuvant chemotherapy followed by surgery
    D. Neoadjuvant chemotherapy followed by radiation

29. A 60-year-old woman with no significant medical history other than a 40 pack-year smoking history has a 2.9-cm lung lesion with no lymph nodes or metastatic disease demonstrated on a screening CT scan. Resection reveals a poorly differentiated squamous cell tumor. Which one of the following is best to recommend for this patient?

    A. Observation therapy with scans in 3 months
    B. Adjuvant radiation therapy
    C. Adjuvant chemotherapy with cisplatin and pemetrexed
    D. Adjuvant chemotherapy with cisplatin and gemcitabine

30. A 45-year-old woman with stage IV adenocarcinoma of the lung presents with a dry cough for 3 months. Her tumor is negative for an *EGFR* mutation and *ALK* or *ROS1*

gene rearrangement. Her medical history includes diet-controlled diabetes and hypertension controlled on lisinopril 20 mg by mouth daily. On the day of treatment, her blood pressure is 130/90 mm Hg and calculated CrCl is 95 mL/minute/1.73 m^2. Which one of the following is best to recommend for this patient?

A. Carboplatin and pemetrexed
B. Cisplatin, pemetrexed, and bevacizumab
C. Carboplatin, paclitaxel, and bevacizumab
D. Cisplatin and gemcitabine

31. A 67-year-old man with stage IV adenocarcinoma of the lung currently receives treatment with carboplatin and pemetrexed. After his sixth cycle, his CT scan reveals stable disease. Which one of the following is best to recommend for this patient?

A. Continue with carboplatin and pemetrexed for two more cycles.
B. Continue with pemetrexed continuation maintenance therapy.
C. Add bevacizumab and continue pemetrexed therapy.
D. Change to bevacizumab maintenance therapy.

32. A 69-year-old man with stage IV squamous cell lung cancer is about to start treatment with albumin-bound paclitaxel and carboplatin. According to investigators, which one of the following is most likely to be improved because of this patient's treatment with albumin-bound paclitaxel instead of conventional paclitaxel?

A. Progression-free survival
B. Overall survival
C. Overall response rate
D. Time to tumor response

33. A 38-year-old woman has newly diagnosed *ALK*-positive stage IV adenocarcinoma. She is currently asymptomatic. Which one of the following regimens is the best first-line therapy for this patient?

A. Cisplatin and pemetrexed
B. Ceritinib
C. Alectinib
D. Crizotinib

34. A 68-year-old woman with a medical history of COPD and controlled hypertension is preparing to start chemotherapy for metastatic squamous cell of the lung. Which one of the following chemotherapy regimens would be most appropriate for initial therapy for her adenocarcinoma?

A. Cisplatin, gemcitabine
B. Cisplatin, gemcitabine, and bevacizumab
C. Cisplatin, pemetrexed
D. Cisplatin, pemetrexed, and bevacizumab

35. A woman has just started treatment with second-line ramucirumab and docetaxel therapy for stage IV adenocarcinoma NSCLC. She has a medical history of hypertension, diabetes, and asthma. Which one of the following is most important to monitor in this patient?

A. Elevation in blood pressure
B. Decrease in thyroid stimulating hormone
C. Elevation in blood glucose
D. Decrease in blood glucose

36. A 52-year-old woman with an exon 19 deletion has been treated with erlotinib for 3 years. Most recent scans revealed new metastatic lesions to the liver; on biopsy, they showed a T790M mutation. Which one of the following is best to recommend for this patient?

A. Give gefitinib.
B. Give afatinib.
C. Give osimertinib.
D. Add chemotherapy to erlotinib.

37. A 45-year-old woman with *ALK*-positive adenocarcinoma of the lung has been treated with crizotinib therapy. Initially, she had mild halo vision, but this went away over time. After having new mild blurry vision, a brain MRI revealed several lesions consistent with metastatic disease. Which one of the following is best to recommend for this patient?

A. Start whole brain radiation.
B. Continue with crizotinib.
C. Change to alectinib therapy.
D. Start carboplatin and pemetrexed.

38. A 58-year-old man with stage IV adenocarcinoma of the lung has recently progressed disease after receiving chemotherapy with carboplatin and pemetrexed. His medical history is significant for diabetes, uncontrolled hypertension, and rheumatoid arthritis requiring current treatment with infliximab and methotrexate. A repeat biopsy was negative for *EGFR*, *ALK*, and *ROS1* but was greater than 50% positive for PD-L1. Which one of the following is best to recommend for this patient?

A. Docetaxel monotherapy
B. Docetaxel and ramucirumab
C. Nivolumab
D. Pembrolizumab

39. A 68-year-old man with adenocarcinoma of the lung receives therapy with pembrolizumab. He is admitted to the hospital with an acute kidney injury and more than 20 loose stools per day. His WBC is normal, and he is afebrile. Which one of the following is best to recommend for this patient?

A. Loperamide
B. Methylprednisolone
C. Tincture of opium
D. Metronidazole

40. A 69-year-old man has recently progressive squamous cell NSCLC after combination chemotherapy with cisplatin and gemcitabine. His oncologist asks for a new biopsy to determine the percentage of PD-L1 overexpression. The patient declines a biopsy and continues with treatment. Which one of the following is best to recommend for this patient?

A. Docetaxel and ramucirumab
B. Pembrolizumab
C. Nivolumab
D. Cisplatin and gemcitabine

Learner Chapter Evaluation: Lung Cancer.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Design a treatment plan for a patient with small cell lung cancer.
31. Evaluate the role of mutational analysis in patients with non–small cell lung cancer.
32. Design a treatment plan for a patient with non–small cell lung cancer.
33. Develop a treatment algorithm for a patient with metastatic non–small cell lung cancer with epidermal growth factor receptor mutation–positive disease, anaplastic lymphoma kinase rearrangement, or ROS proto-oncogene 1 rearrangement.
34. Assess the impact of adding vascular endothelial growth factor receptor inhibitors in non–small cell lung cancer.
35. Examine the role of immunotherapy in the treatment of metastatic non–small cell lung cancer.

Questions 36–38 apply to the entire learning module.

36. How long did it take you to read the instructional materials in this module?
37. How long did it take you to read and answer the assessment questions in this module?
38. Please provide any additional comments you may have regarding this module:

Oncologic Care II

Oncologic Care II Panel

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Toxicities of Targeted Oral Chemotherapy

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Toxicities of Oral Targeted Chemotherapy

By Lisa K. Lohr, Pharm.D., BCPS, BCOP

Reviewed by Robert Mancini, Pharm.D., BCOP; Tristan Lindfelt, Pharm.D., BCPS, BCOP, BCACP; and Eva Y. Wong, Pharm.D., BCPS, BCACP, CDE

LEARNING OBJECTIVES

1. Distinguish between the epidermal growth factor receptor (EGFR)/MAPK/ERK kinase (MEK) inhibitor rash and the hand-foot skin reaction, given symptomatology, and design appropriate prevention and management regimens.
2. Evaluate preventive strategies for agents associated with photosensitivity.
3. For the patient taking oral targeted treatment, assess the risk of QTc prolongation given concomitant medications and comorbidities, and devise a risk management plan.
4. Develop monitoring and treatment plans for vascular endothelial growth factor inhibitor–induced hypertension and left ventricular ejection fraction dysfunction.
5. Construct monitoring plans, treatment goals, and therapy plans for hypothyroidism, hyperlipidemia, and hyperglycemia associated with oral targeted cancer treatment.

ABBREVIATIONS IN THIS CHAPTER

EGFR	Epidermal growth factor receptor
HF	Heart failure
HFSR	Hand-foot skin reaction
HG	Hyperglycemia
HoT	Hypothyroidism
HTN	Hypertension
LVD	Left ventricular dysfunction
LVEF	Left ventricular ejection fraction
MEK	MAPK/ERK kinase (mitogen-activated protein kinase/extracellular-regulated kinase)
mTOR	Mammalian target of rapamycin
TdP	Torsades de pointes
TSH	Thyroid-stimulating hormone
VEGF	Vascular endothelial growth factor
VSP	Vascular endothelial growth factor signaling pathway

Table of other common abbreviations.

INTRODUCTION

The use of oral targeted cancer treatment has risen exponentially since imatinib received FDA label approval in 2001. Targeted cancer treatments have revolutionized the treatment of some cancers and have different spectra of toxicities. Other oral chemotherapy treatments (e.g., chlorambucil, melphalan) were developed in the early phases of cancer chemotherapy; they have conventional chemotherapy mechanisms of action related to the inhibition of DNA and RNA function and replication. In contrast, oral targeted cancer treatments block the alterations in the cancer cell that make it malignant.

Many cancer cells have altered intracellular mechanisms because of mutations that lead to increased cellular differentiation, proliferation, inhibition of apoptosis, and enhanced survival. Oral targeted cancer agents block these altered intracellular pathways, leading to the antitumor action. Some of these targets include transmembrane and intracellular tyrosine kinases that lead to abnormal downstream effects. Other targeted agents induce cancer cell maturation to noncancerous cells, whereas others target non–tyrosine kinase mechanisms. These pathways include vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), and mammalian target of rapamycin (mTOR) pathways.

Oral targeted cancer agents are used in many different situations. They are used in the treatment of different types of cancer, including solid tumors, leukemias, and lymphomas. Some are used in chronic treatment, and others are used short term. Some agents are indicated for first-line treatment, some for adjuvant treatment after surgery or

radiation, and others for refractory cancers. Some targeted treatments are used alone, whereas others are prescribed together with other oral targeted treatments or with intravenous or injectable chemotherapy. Some are indicated for continuous treatment (until disease progression or intolerable adverse effects develop), and others are given in a cyclical fashion (e.g., 3 weeks on, then 1 week off, then repeat).

Unfortunately, oral targeted cancer treatments are associated with adverse effects that, if uncontrolled, limit the ability of the patient with cancer to continue the treatment. Conventional chemotherapy adverse effects (e.g., nausea, myelosuppression, mucositis) sometimes occur with some of the oral targeted treatments but are usually not dose limiting. Oral targeted cancer treatments also result in toxicities that are uncommon in conventional chemotherapy agents and can be dose limiting and require different management practices. Treating these adverse effects, including dermatologic, cardiovascular, and metabolic toxicities, is crucial to enabling a patient to stay on potentially lifesaving cancer treatments. Monitoring for and managing these adverse effects requires collaboration between primary care practitioners and the oncology care team.

The National Cancer Institute Common Terminology Criteria for Adverse Effects are commonly used to describe the severity of cancer treatment toxicity. Grade 1 and grade 2 toxicities are mild, grade 3 toxicities are moderate, and grade 4 toxicities are severe. Grade 3 and grade 4 adverse effects are commonly counted together because they often are dose limiting and may require dose modification or discontinuation of the cancer treatment.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge about the pathophysiology of hypertension, left ventricular dysfunction/heart failure, hypothyroidism, hyperlipidemia, and diabetes
- Pharmacology of standard treatments for hypertension, left ventricular dysfunction/heart failure, hypothyroidism, hyperlipidemia, and diabetes

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults. JAMA 2014;311:507-20.
- 2013 ACCF/AHA guideline for the management of heart failure. Circulation 2013;128:C420-E327.
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- National Lipid Association. Recommendations for patient-centered management of dyslipidemia. Part 1. J Clin Lipidol 2015;9:129-69.
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- Diagnosis and management of diabetes: synopsis of the 2016 American Diabetes Association standards of medical care in diabetes. Ann Intern Med 2016;164:542-52.
- American Cancer Society [homepage on the Internet].
- National Comprehensive Cancer Network [homepage on the Internet].

DERMATOLOGIC ADVERSE EFFECTS FROM ORAL TARGETED CHEMOTHERAPY

Acneiform Papulopustular Rash Caused by EGFR and MEK Inhibitors

Pharmacology and Mechanism of Toxicity

Inhibitors of the EGFR pathway are associated with several dermatologic adverse effects. These include a papulopustular eruption, paronychia, xerosis, changes in hair texture and growth, and pruritus. The two classes of EGFR inhibitors are oral tyrosine kinase inhibitors and intravenous monoclonal antibodies. The EGFR-related dermatologic toxicities occur with both classes. The EGFR pathway is involved in homeostasis of the epidermis through stimulation of keratinocyte proliferation and maturation (Califano 2015; Macdonald 2015a; Kyllo 2014). In addition, inhibitors of the MAPK/ERK kinase (mitogen-activated protein kinase/extracellular-regulated kinase, or MEK) pathway can result in a papulopustular eruption.

The most common and most clinically significant dermatologic adverse effect is the papulopustular eruption that occurs in a seborrheic distribution (scalp, face, upper chest, and back) (Macdonald 2015a; Kyllo 2014; Lacouture 2011). The eruption consists of tender and erythematous follicle-based papules and pustules accompanied by pain, burning, and irritation and can result in crusting of ruptured pustules.

Table 1-1. Oral Targeted Chemotherapy Agents Associated with EGFR/MEK Acneiform Papulopustular Rash

Drug	Indication	Overall Frequency	Grade 3/4 Frequency
Afatinib	NSCLC	+++++	++++
Cabozantinib	Thyroid cancer and kidney cancer	+++	+
Cobimetinib	Melanoma	+++	++
Erlotinib	NSCLC	+++++	++
Gefitinib	NSCLC	+++++	++
Lapatinib	Breast cancer	+++ to ++++	++
Osimertinib	NSCLC	++++	++
Sorafenib	Kidney cancer and liver cancer	+++ to ++++	++
Sunitinib	GIST, kidney cancer, and pancreatic neuroendocrine cancer	+++	++
Trametinib	Melanoma	+++	+
Vandetanib	Thyroid cancer	+++ to ++++	++

EGFR = epidermal growth factor receptor; GIST = gastrointestinal stromal tumor; MEK = MAPK/ERK kinase; NSCLC = non–small cell lung cancer.

+++++ = > 50%; ++++ = 30%–50%; +++ = 10%–30%; ++ = 1%–10%; + = < 1%.

Information from: UpToDate, Micromedex, package inserts, and literature sources.

Bacterial superinfections may occur. Papulopustular eruptions have also been described as an acneiform rash and inflammatory folliculitis. Although similar in appearance to acne, papulopustular eruptions do not have comedones and are often accompanied by pruritus. The onset of this reaction is usually within 1–2 weeks of therapy initiation and can be dose related.

Papulopustular eruptions often occur on the face; they can have significant psychosocial impact, decreasing quality of life, and can lead patients to discontinue potentially effective treatment (Brown 2016; MacDonald 2015a). The presence and severity of the rash in patients who persisted with the treatment have been associated with longer progression-free survival and overall survival in patients with non–small cell lung cancer (Faehling 2010). It is important to adequately treat this condition to allow patients to continue the EGFR inhibitor long enough to achieve the clinical benefits (Brown 2016; MacDonald 2015a).

Oral Targeted Chemotherapy Agents Involved

The oral targeted cancer treatments associated with the EGFR and MEK papulopustular rash are shown in Table 1-1.

Assessment and Grading

The oncology grading criteria for this eruption are described in Box 1-1. In papulopustular eruption, patients may find a low-grade reaction very significant, given its impact on their quality of life.

Box 1-1. NCI CTCAE Acneiform Rash Grading Criteria

Grade 1
- Papules and/or pustules covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness

Grade 2
- Papules and/or pustules covering 10%–30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLs

Grade 3
- Papules and/or pustules covering > 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADLs; associated with local superinfection with oral antibiotics indicated

Grade 4
- Papules and/or pustules covering any percentage of the BSA, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with intravenous antibiotics indicated; life-threatening consequences

Grade 5
- Death

ADLs = activities of daily living; BSA = body surface area; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Effects.

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

Prevention and Treatment

Good skin care forms the basis for preventing the EGFR/MEK eruption (Box 1-2). Recommendations include using moisturizers and sunscreen and avoiding skin irritants (e.g., regular soap, hot water). Some authors suggest using topical hydrocortisone 1% once or twice daily (Brown 2016; Lacouture 2011; Hofheinz 2016). Several studies have looked at oral tetracycline antibiotics, which are used primarily for their anti-inflammatory properties, as a preventive strategy. In short, however, these studies have had conflicting results, with some showing a positive impact on prevention and others, no statistically significant impact (Kyllo 2014; Reguiai 2012). The most recent of these studies (Melosky 2016) investigated prophylactic treatment with minocycline 100 mg twice daily for 6 weeks in patients starting erlotinib compared with the usual reactive treatment if eruption developed of topical clindamycin and hydrocortisone with or without minocycline. The incidence of papulopustular eruption did not differ between the groups. In clinical practice, prophylactic treatment with minocycline or doxycycline is still sometimes offered to patients, especially if they are reluctant to start cancer treatment because of this reaction or if they have had the reaction to previous cancer treatment.

Box 1-2. EGFR/MEK Rash Prevention Strategies

- Hydrocortisone 1% cream once or twice daily
- Moisturizer and sunscreen twice daily (SPF ≥25)
- Avoidance of skin irritants
- Minocycline 100 mg daily or doxycycline 100 mg once or twice daily

For treatment of papulopustular eruptions, the literature has many sets of recommendations but few randomized controlled trials. However, many studies recommend similar treatments that include topical corticosteroids and oral minocycline or doxycycline. Treatments that are no longer recommended include topical calcineurin inhibitors, retinoids, and OTC acne treatments because they are either too irritating or ineffective. Common recommendations for treatment of papulopustular eruptions are shown in Table 1-2.

The papulopustular eruption is often preceded or accompanied by significant pruritus. Treating the eruption itself will help relieve the itching. Medications such as hydroxyzine or second-generation antihistamines can be very helpful. For refractory pruritus, gabapentin, pregabalin, or low-dose doxepin is recommended (Macdonald 2015a; Lacouture 2011). In addition, significant xerosis can occur and may only develop after 1–3 months on treatment (Macdonald 2015a). With xerosis, as with topical treatment of the papulopustular rash, attention should be paid to the vehicle of the product. All skin products should be alcohol free. Water-based creams and lotions may be more drying to the skin, but the thicker, richer emollients may exacerbate the folliculitis. It is important to balance the product to the individual patient's needs (Macdonald 2015a).

Hand-Foot Skin Reaction

Pharmacology and Mechanism of Toxicity

Some patients treated with oral targeted cancer treatments can have a painful skin disorder called hand-foot skin reaction (HFSR). It is characterized by tingling, burning pain; erythema; blisters; and hyperkeratotic and desquamating areas,

Table 1-2. Recommended Treatments for EGFR/MEK Papulopustular Eruption

Grade 1	Hydrocortisone 1%–2.5% topically BID plus Clindamycin 1% topically BID
Grade 2	Continue as above plus Doxycycline 100 mg PO BID or minocycline 100 mg PO daily
Grade 3	Continue as above plus Consider oral corticosteroids Temporarily hold the EGFR inhibitor until symptoms improve; consider reinitiating at a lower dose
Grade 4	Permanently discontinue EGFR inhibitor and refer to dermatologist and/or burn center

BID = twice daily; PO = orally.

Information from: Brown J, Su Y, Nellesen D, et al. Management of epidermal growth factor receptor inhibitor-associated rash: a systematic review. J Comm Support Onc 2016;14:21-8; Califano R, Tariq N, Compton S, et al. Expert consensus on the management of adverse events from EGFR tyrosine kinase inhibitors in the UK. Drugs 2015;75:1335-48; Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079-95; Macdonald JB, Macdonald B, Golitz LE, et al. Cutaneous adverse effects of targeted therapies part I: inhibitors of the cellular membrane. J Am Acad Dermatol 2015;72:203-18; and Reguiai Z, Bachet JB, Bachmeyer C, et al. Management of cutaneous adverse events induced by anti-EGFR (epidermal growth factor receptor): a French interdisciplinary therapeutic algorithm. Support Care Cancer 2012;20:1395-404.

primarily on the palms of the hands and soles of the feet. Symptom onset is usually in the first 2 months or cycles, often in the first 2–4 weeks, and may be more severe or more prevalent in those treated with a higher dose of oral targeted cancer agent. The hands and feet seem to be targeted because these are areas of almost constant pressure and friction. The mechanism of HFSR may be related to inhibition of healing of blood vessel micro-trauma caused by VEGF receptor or platelet-derived growth factor receptor inhibition (Macdonald 2015a; Macdonald 2015b; McLellan 2015; Kyllo 2014).

Hand-foot skin reaction symptoms can range from mild discomfort to severe pain and the inability to walk or use the hands for activities of daily living. When symptoms are severe, dose adjustments or drug discontinuation may be necessary. Uncontrolled symptoms may lead the patient to decline further cancer treatment.

Hand-foot skin reaction is similar to the hand-foot syndrome that occurs with cancer treatments (both oral and intravenous) with conventional chemotherapy mechanisms of action, but with some subtle differences. *Palmar-plantar erythrodysesthesia* is an umbrella term describing both conditions.

Oral Targeted Chemotherapy Agents Involved

The oral targeted cancer treatments associated with HFSR are shown in Table 1-3. These agents include VEGF receptor inhibitors and multikinase inhibitors.

Assessment and Grading

There is no set of oncology grading criteria specific for HFSR. In practice, the grading criteria for palmar-plantar erythrodysesthesia are used for HFSR. These criteria are shown in Box 1-3.

Box 1-3. NCI CTCAE Hand-Foot Skin Reaction Grading Criteria

Grade 1
- Minimal skin changes or dermatitis (erythema, edema, or hyperkeratosis)

Grade 2
- Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting instrumental ADLs

Grade 3
- Skin changes (peeling, blisters, bleeding, edema, or hyperkeratosis) with pain, limiting self-care ADLs

Grade 4
- N/A

Grade 5
- N/A

N/A = not applicable.

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

Prevention and Treatment

Good skin care and avoidance of friction and pressure form the basis for preventing HFSR symptoms (Macdonald 2015a, 2015b; McLellan 2015; Kyllo 2014). Emollient skin creams (thick creams instead of thin lotions) should be applied often to hands and feet. Advise patients to wear shoes that fit well (avoid pinching or rubbing) with cushioned insoles or padded

Table 1-3. Oral Targeted Chemotherapy Agents Associated with HFSR

Drug	Indication	Overall Frequency	Grade 3/4 Frequency
Axitinib	Kidney cancer	+++	++
Cabozantinib	Thyroid cancer, kidney cancer	++++	++ to +++
Dabrafenib	Melanoma	+++	++
Lapatinib	Breast cancer	+++++	++
Lenvatinib	Thyroid cancer	++++	++
Pazopanib	Kidney cancer, soft tissue sarcoma	++ to +++	++
Regorafenib	Colorectal cancer, GIST	++++ to +++++	+++
Sorafenib	Liver cancer, kidney cancer, thyroid cancer	+++++	+++
Sunitinib	GIST, kidney cancer, pancreatic neuroendocrine cancer	+++	++
Vemurafenib	Melanoma	++	NR

HFSR = hand-foot skin reaction; NR = not reported.

Information from: UpToDate, Micromedex, package inserts, and literature sources.

or gel-filled inserts. Wearing cotton socks will help reduce friction. If patients have hyperkeratotic areas on the feet at baseline, referral to a podiatrist is warranted. Patients should avoid hot water and harsh soaps or detergents. Patients may prefer wearing cotton gloves to keep the emollients on the skin and protect the skin of the hands.

Urea-based creams have both emollient and keratolytic qualities. A recent trial studied a urea-based cream used for HFSR prophylaxis in patients with liver cancer starting sorafenib (Ren 2015). In this trial, those in the study group received urea 10% cream applied to hands and feet three times daily plus best supportive care. Those in the control group received best supportive care alone. The incidence of all-grade HFSR was 56% in the urea-treated group compared with 73.6% in the control. In addition, the incidence of grade 2 and grade 3 HFSR was 20.7% in the urea group compared with 29.2% in the best supportive care–only group.

Treatment of established HFSR may include topical corticosteroids, topical or systemic analgesics, and dose interruption and dose modification of the oral cancer treatment. There are no standard, universally accepted treatment algorithms, but many experts recommend the common treatments shown in Table 1-4.

Photosensitivity

Pharmacology and Mechanism of Toxicity

Some oral targeted treatments are associated with photosensitivity, an unusual sensitivity of the skin to UV light. In these cases, patients can develop severe sunburn from less than 15 minutes of sunlight exposure, or with minimal sun intensity or exposure through window glass (Macdonald 2015b; Hagen 2014). The reaction is a typical, but often severe, sunburn with rapid painful erythema and blister formation (Box 1-4).

Box 1-4. NCI CTCAE Photosensitivity Grading Criteria

Grade 1
- Painless erythema and erythema covering < 10% BSA

Grade 2
- Tender erythema covering 10%–30% BSA

Grade 3
- Erythema covering > 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid indicated; pain control indicated (narcotics or NSAIDs)

Grade 4
- Life-threatening consequences; urgent intervention indicated

Grade 5
- Death

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

Vemurafenib is one of the agents with higher rates of photosensitivity. This can develop in the first 2 weeks of treatment. With vemurafenib, the reaction is primarily an excessive sensitivity to UVA (which can penetrate window glass) but not UVB (Macdonald 2015b; Hagen 2014). It is unclear whether this is also true for the other oral targeted chemotherapy agents.

Oral Targeted Chemotherapy Agents Involved

Most of the oral targeted chemotherapy agents involved are inhibitors of MEK or the BRAF (B-rapidly accelerated fibrosarcoma kinase). These agents are shown in Table 1-5.

Table 1-4. Treatment of HFSR

Grade 1	Continue good skin care Add urea-based cream 10%–20% at least BID No change in cancer treatment dose
Grade 2	Add clobetasol 0.05% topically once or twice daily Continue urea-based cream 20% at least BID Consider holding cancer treatment temporarily
Grade 3	Hold cancer treatment, may reinitiate at lower dose once symptoms resolve to ≤ grade 2 Continue clobetasol as above May increase urea-based cream to 20%–40% Consider topical lidocaine, systemic NSAIDs, gabapentin, pregabalin, or opioids

Information from: Kyllo RL, Anadkat MJ. Dermatologic adverse events to chemotherapeutic agents, part I: cytotoxic agents, epidermal growth factor inhibitors, multikinase inhibitors and proteosome inhibitors. Sem Cutan Med Surg 2014;33:28-39; Macdonald JB, Macdonald B, Golitz LE, et al. Cutaneous adverse effects of targeted therapies part I: inhibitors of the cellular membrane. J Am Acad Dermatol 2015;72:203-18; Macdonald JB, Macdonald B, Golitz LE, et al. Cutaneous adverse effects of targeted therapies: part II inhibitors of intracellular molecular signaling pathways. J Am Acad Dermatol 2015;221-36; and McLellan B, Ciardiello F, Lacouture ME, et al. Regorafenib-associated hand-foot skin reaction: practical advice on diagnosis, prevention, and management. Ann Oncol 2015;26:2017-26.

Table 1-5. Oral Targeted Chemotherapy Agents Associated with Photosensitivity

Drug	Indication	Overall Frequency	Grade 3/4 Frequency
Cobimetinib	Melanoma	++++	++
Dabrafenib	Melanoma	++	NR
Imatinib	CML, Ph+ ALL, GIST	++	NR
Vandetanib	Thyroid cancer	+++	+++
Vemurafenib	Melanoma	++++	++

CML = chronic myeloid leukemia; NR = not reported; Ph+ ALL = Philadelphia chromosome–positive acute lymphoid leukemia.

Information from: UpToDate, Micromedex, package inserts, and literature sources.

Prevention and Treatment

It is critical to advise patients on how to prevent these sunburns. This should include avoiding sunlight, wearing clothing/hats with adequate sun protection, and applying sunscreen with a sun protection factor (SPF) of 30 or greater (Macdonald 2015b; Hagen 2014). A sunscreen must be chosen that protects against UVA and UVB because many available products do not have both. Products containing oxybenzone, sulisobenzone or dioxybenzone, avobenzone, ecamsule, and titanium dioxide or zinc oxide provide UVA protection. Para-aminobenzoic acid, padimate, octinoxate, cinoxate octisalate, homosalate, and trolamine salicylate do not provide UVA protection. Patients should also be reminded to apply enough of the product (at least 1 oz) often (every 2 hours and after swimming or sweating). In addition, it may be good to use UVA-blocking window screens in the patient's car as well as in the home and office, where exposure is likely.

If a patient does develop a significant sunburn, it should be treated like other sunburns. Cool, wet topical dressings; topical emollients; and systemic analgesics are recommended. For severe sunburns, topical or systemic corticosteroids and antihistamines may be necessary.

CARDIAC ADVERSE EFFECTS FROM ORAL TARGETED CHEMOTHERAPY

Hypertension Induced by VEGF Signaling Pathway Inhibitors

Pharmacology and Mechanism of Toxicity

Hypertension (HTN) is associated with several oral targeted cancer treatments, and the class of agents with the highest incidence of HTN is the VEGF signaling pathway (VSP) inhibitors. The VEGF pathway is vital for the maintenance of blood vessels in the body, leading to nitric oxide production (vasodilation) and angiogenesis. Vascular adverse effects of VSP inhibitors have been reported with all of these agents, with HTN the most commonly reported. The VSP inhibitors are thought to lead to HTN through increased vascular resistance by decreasing nitric oxide production, endothelial cell disruption, and capillary rarefaction (a decrease in the functional vessels in capillary beds).

Blood pressure elevations can occur in patients with or without preexisting HTN. Elevations can develop quite quickly and are usually apparent in the first 2 months of treatment with VSP inhibitors. They can even arise in the first week of therapy in some cases. The elevations can be significant, with increases in systolic blood pressure or diastolic blood pressure of 10–30 mm Hg. Some patients are at greater risk of developing VSP-induced HTN. These include patients with (1) older age, (2) obesity, and (3) preexisting HTN (Hamnvik 2015).

Oral Targeted Chemotherapy Agents Involved

Table 1-6 lists the VSP inhibitors most commonly associated with HTN.

Assessment and Grading

The standard oncology grading criteria applicable to HTN are shown in Box 1-5. Grade 1 HTN is analogous to prehypertension. Grade 2 and grade 3 HTN correspond with stage 1 and stage 2 HTN.

Monitoring Plans

Patients at a higher risk of the consequences of uncontrolled HTN with VSP inhibitors include those with (1) grade 3 or grade 4 HTN, (2) diabetes, (3) established cardiovascular disease, and (4) established or subclinical renal disease (Maitland 2010). Many patients treated with oral VSP inhibitors have kidney cancer and have already had a nephrectomy in their treatment course. Patients having only one kidney may be more sensitive to the renal effects of antihypertensive treatment.

Table 1-6. Oral Targeted Chemotherapy Agents Associated with HTN

Drug	FDA Label-Approved Indications	Overall Frequency	Grade 3/4 Frequency
Axitinib	Kidney cancer	++++	+++
Cabozantinib	Thyroid cancer, kidney cancer	++++	++
Lenvatinib	Thyroid cancer	+++++	++++
Pazopanib	Kidney cancer, soft tissue sarcoma	++++	++
Ponatinib	Ph^+ ALL, CML	+++++	++++
Regorafenib	Colorectal cancer, GIST	++++ to +++++	++ to +++
Sorafenib	Liver cancer, kidney cancer, thyroid cancer	+++	++
Sunitinib	GIST, kidney cancer, pancreatic neuroendocrine cancer	+++ to ++++	++ to +++
Vandetanib	Thyroid cancer	++++	++

Information from: UpToDate, Micromedex, package inserts, and literature sources.

The appropriate blood pressure goals for patients with VSP inhibitor–induced HTN are no different from those for the general population, and no evidence supports different goal blood pressure ranges. The 2014 Eighth Joint National Committee (James 2014) guidelines should apply. Most people with cancer are older, and the patients for whom the blood pressure goal of less than 150/90 mm Hg is applicable will depend on an assessment of the patient's overall health condition and risk of falls. In addition, some patients treated with VSP inhibitors may have a limited life expectancy or other comorbidities that make the goal of less than 150/90 mm Hg more appropriate.

Patients starting VSP treatment should have their blood pressure and cardiovascular risk history assessed before initiation. Many people presenting for oncology care have undiagnosed or undertreated HTN at baseline. Preexisting blood pressure elevations should be controlled before beginning treatment with VSP inhibitors (Maitland 2010).

Monitoring for VSP inhibitor–induced HTN should begin with the start of treatment. In-clinic and home blood pressure monitoring have both advantages and disadvantages. Many patients seen in the oncology clinic are under emotional stress, and many elevations in blood pressure are dismissed. Often, the oncology clinic is far from their home, and returning often to the clinic for blood pressure monitoring is difficult. Patients may be seen at their local clinic or pharmacy for blood pressure readings. For some patients, home blood pressure monitoring is useful. This allows for more frequent measurements at different times of the day. However, not all home blood pressure monitors have acceptable accuracy. In practice, reviewing both clinic- and home-based measurements is needed (Maitland 2010).

For patients who can come to the clinic often, blood pressure should be monitored weekly with a VSP inhibitor for the first month of treatment, every 2 weeks for the second and third months, and then as indicated, depending on the appearance of HTN. For patients relying on home monitoring, blood pressure should be measured daily or at least two or three times per week, with telephone follow-up with a health care practitioner. Patients should be advised to report any blood pressure readings greater than 160/100 mm Hg and those

Box 1-5. NCI CTCAE HTN Grading Criteria

Grade 1
- SBP 120–139 mm Hg or DBP 80–89 mm Hg

Grade 2
- SBP 140–159 mm Hg or DBP 90–99 mm Hg; or symptomatic DBP increase by > 20 mm Hg; monotherapy indicated

Grade 3
- SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg; more than one drug or more intensive therapy than previously used indicated

Grade 4
- Life-threatening consequences (malignant HTN, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated

Grade 5
- Death related to HTN

DBP = diastolic blood pressure; HTN = hypertension; SBP = systolic blood pressure.

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

consistently greater than 140/90 mm Hg. Some researchers also consider the magnitude of the blood pressure elevations, regardless of the starting blood pressure value (Maitland 2010). Diastolic blood pressure elevations of greater than 20 mm Hg should be assessed for blood pressure treatment.

Antihypertensive Treatment Recommendations

Treating the blood pressure elevations is critical to maintaining the cancer treatment regimen. Uncontrolled HTN can lead to complications such as heart failure (HF), stroke, myocardial infarction, and renal impairment, as well as other neurological complications such as reversible posterior leukoencephalopathy syndrome. This is true for people being treated with oral targeted cancer treatments as well as for the general population. Some patients receiving these agents have a limited life expectancy, but for others, life expectancy can be quite long with continued treatment. Although data are conflicting, some researchers suggest that patients who have VSP inhibitor–induced HTN have a longer average survival than those who do not, indicating potent VSP inhibition (Suter 2013; Izzedine 2009). Keeping the blood pressure under control will allow patients to remain on the cancer treatment for as long as possible to gain its benefits (O'Hare 2015; Senkus 2011; Maitland 2010; Izzedine 2009).

In large part, treatment of VSP inhibitor–induced HTN is the same as treatment of HTN in the general population. However, there are a few extra considerations. Lifestyle changes are not likely to be effective rapidly enough. Exercising is difficult for patients with cancer-related fatigue, although increasing physical activity is one of the best treatments for fatigue. Many patients with cancer unintentionally lose weight, and dietary restrictions may worsen this. Because the underlying mechanism of VSP inhibitor–induced HTN is potent vasoconstriction, monotherapy with a thiazide-type diuretic is unlikely to be effective. These patients are also at risk of dehydration because of emesis and diarrhea and poor oral fluid intake (Suter 2013; Izzedine 2009).

Some retrospective case-control studies have shown that in kidney cancer and VSP inhibitor–induced HTN, patients treated with angiotensin system inhibitors had improved overall survival compared with patients treated with other types of antihypertensive treatments (Izzedine 2015; McKay 2015). In the absence of contraindications, angiotensin system inhibitors are good choices for treatment.

Most of the oral VSP inhibitors are metabolized by the CYP3A4 enzymatic system of the liver. Verapamil and diltiazem are inhibitors of CYP3A4 and are best avoided during treatment to reduce the other toxicity of VSP inhibitors. There is some evidence that nifedipine can induce VEGF secretion, potentially reducing the antitumor effect of VSP inhibitors (Abi Aad 2015; Izzedine 2009). Because of this, nifedipine is not recommended to treat VSP inhibitor–induced HTN.

For most patients, treatment should begin with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or a dihydropyridine calcium channel blocker (amlodipine or felodipine) (Maitland 2010; Izzedine 2009). The ACE inhibitors can work more quickly than the calcium channel blockers. With ACE inhibitors, it is important to monitor renal function and potassium concentration 1–2 weeks after initiation, especially in patients who have had a nephrectomy (Snively 2004). After initiating an antihypertensive agent, it is important to monitor blood pressure often and, if not within goal, to advance the dose of the antihypertensive agent as soon as the full effects occur, once or twice per week. It is important to achieve blood pressure within the goal as soon as possible so that the cancer treatment can proceed. A second and potentially third antihypertensive agent may be required. If the patient's blood pressure exceeds 160/100 mm Hg with confirmed readings, it may be necessary to discontinue the VSP inhibitor until blood pressure control can be regained, but time without anticancer treatment should be minimized. If the patient has other medical conditions such as HF or cardiac arrhythmias, other antihypertensive agents may be used.

In rare cases when blood pressure cannot be maintained at goal, the dose of the VSP inhibitor may need to be decreased, but this approach has the possibility of inadequate cancer treatment. If the VSP inhibitor must be discontinued for toxicity or ineffectiveness, the blood pressure elevations should dissipate in most cases. These patients should be monitored carefully to determine whether the blood pressure medications can be discontinued.

In summary, HTN associated with VSP inhibitor treatment is common and can develop quickly. Patients should have close follow-up for blood pressure control. Angiotensin system inhibitors and dihydropyridine antihypertensive agents are usually the first agents to start. After rapidly advancing the dose, additional antihypertensive agents may be needed. Controlling blood pressure can allow these patients to benefit from treatment with VSP inhibitors.

Left Ventricular Dysfunction and HF

Pharmacology and Mechanism of Toxicity

Several oral targeted cancer treatments have been associated with left ventricular dysfunction (LVD) or HF. These include agents with a variety of molecular targets, and many affect multiple pathways. The mechanism of this toxicity has not been fully described and may be different depending on the molecular targets involved. Human epidermal growth factor receptor 2 VEGF and platelet-derived growth factor receptor play a substantial role in cardiovascular health. Some of the postulated mechanisms include mitochondrial dysfunction and systemic vasoconstriction.

Oral Targeted Chemotherapy Agents Involved

Table 1-7 shows the agents associated with LVD or HF. The incidence of reported toxicity can vary depending on differing criteria such as whether the cardiac end points were

Table 1-7. Oral Targeted Chemotherapy Agents Associated with LVD or HF

Drug	FDA Label-Approved Indications	LVEF Decline Frequency	Clinically Significant HF Frequency	Manufacturer LVEF Monitoring Recommendations
Axitinib	Kidney cancer	++	++	NR
Cobimetinib	Melanoma	Cardiomyopathy (grade 2 or grade 3) +++		Assess LVEF before therapy initiation, 1 mo after, and every 3 mo thereafter. Also assess LVEF at 2, 4, 10, and 16 wk and then as clinically indicated after dose reduction or treatment interruption
Dasatinib	Ph^+ ALL, CML	++	+	NR
Lapatinib	Breast cancer	++	+	Baseline and periodic LVEF evaluations are recommended
Lenvatinib	Thyroid cancer	Cardiac failure ++	NR	NR
Imatinib	CML, Ph^+ ALL, GIST	++	NR	NR
Pazopanib	Kidney cancer, soft tissue sarcoma	++	NR	Baseline and periodic LVEF monitoring is recommended in patients at increased risk of HF
Ponatinib	Ph^+ ALL, CML	++/+++	++	NR
Regorafenib	Colorectal cancer, GIST	++	NR	NR
Sorafenib	Liver cancer, kidney cancer, thyroid cancer	HF ++		NR
Sunitinib	GIST, kidney cancer, pancreatic neuroendocrine cancer	+++	++ to +++	Obtain LVEF evaluation before treatment and periodically
Trametinib	Melanoma	Cardiomyopathy ++		Assess LVEF before therapy initiation, at 1 mo, and then at 2- to 3-mo intervals while on therapy
Vandetanib	Thyroid cancer	Cardiac failure ++		

HF = heart failure; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction.
Information from: UpToDate, Micromedex, package inserts, and literature sources.

characterized in all patients or just in symptomatic patients, or whether the study used unique definitions of cardiac toxicity. One group defines LVD as a decline in left ventricular ejection fraction (LVEF) of at least 5% to less than 55% with accompanying signs or symptoms, or a decline in LVEF of at least 10% to below 55% without accompanying signs or symptoms (O'Hare 2015). Left ventricular dysfunction associated with these molecularly targeted cancer treatments can occur in the first few months of therapy and is often reversible. Patients at higher risk of developing this toxicity include those with HTN, heart disease, or prior chemotherapy with anthracyclines.

Assessment and Grading

There is no single, accepted methodology to assess LVD caused by oral targeted cancer treatments. However, in most cases, the patient's LVEF is assessed with either echocardiography or a multigated acquisition scan. However, these methods detect cardiac toxicity at a fairly late stage, after other compensatory mechanisms have been depleted. Other methods include cardiac MRI, measurements of global longitudinal cardiac strain, and biomarkers such as cardiac troponins. The standard oncology grading criteria applicable to HF and LVD are shown in Box 1-6. Grade 1 HF corresponds with stage B HF, according to the 2013 American College of

Box 1-6. NCI CTCAE Grading Criteria

Heart Failure

Grade 1
- Asymptomatic with laboratory or cardiac imaging abnormalities

Grade 2
- Symptoms with mild to moderate activity or exertion

Grade 3
- Severe symptoms at rest or with minimal activity or exertion; intervention indicated

Grade 4
- Life-threatening consequences; urgent intervention indicated (continuous intravenous therapy or mechanical hemodynamic support)

Left Ventricular Systolic Dysfunction

Grade 1 N/A

Grade 2 N/A

Grade 3
- Symptomatic because of drop in EF responsive to medications

Grade 4
- Refractory or poorly controlled heart failure because of drop in EF; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplantation indicated

Grade 5 N/A

EF = ejection fraction; N/A = not applicable.
Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines (Yancy 2013). Grade 2 and grade 3 HF and LVD correspond with stage C HF, and grade 4 toxicity corresponds with stage D HF.

Monitoring Plans

There are no published guidelines for monitoring LVD during cancer treatment. For some of the oral targeted cancer treatments associated with LVD or HF, specific monitoring recommendations are provided by the manufacturers (see Table 1-7). However, these recommendations do not always coincide with the frequency or severity of reported toxicity. For agents associated with LVD or HF, it is prudent to monitor LVEF at baseline and periodically during treatment, especially in older patients and those at higher risk.

Treatment

Treatment of oral targeted cancer treatment–induced LVD or HF is no different from treatment of LVD/HF attributable to other causes. Some suggest that all patients receiving these treatments should be treated as stage A according to the 2013 ACCF/AHA guidelines (Yancy 2013). For grade 2 and higher toxicities, multidrug therapy with an ACE inhibitor or ARB together with a β-blocker (bisoprolol, carvedilol, or metoprolol succinate) is appropriate, as for stage B and stage C HF. Loop diuretics should be used to control fluid overload. In most grade 2 or higher toxicities, the targeted cancer treatment should be discontinued permanently.

QT Prolongation

Pharmacology and Mechanism of Toxicity

During each heartbeat, the cardiac ventricles undergo activation and recovery, depolarization, and then repolarization, which are depicted on the surface ECG as the QT interval (the duration of the action potential) (Kim 2014). The QT interval is highly dependent on the heart rate, and several correction equations are available, with no clear-cut standard. In men, the normal QTc interval is less than 430 milliseconds, and greater than 470 milliseconds is considered prolonged. In women, the QTc is usually longer, with normal ranges less than 450 milliseconds and greater than 480 milliseconds considered prolonged. Any QTc greater than 500 milliseconds is defined as highly abnormal.

Prolonged QTc intervals have been associated with serious cardiac ventricular tachyarrhythmias, the most common of which is torsades de pointes (TdP). Torsades de pointes may be asymptomatic or the patient may faint, and TdP is usually transient. When it persists, TdP may deteriorate into ventricular fibrillation, which can result in sudden cardiac death. Although a prolonged QTc interval is an inadequate predictor of TdP development, it is regarded as the best surrogate marker available (Locatelli 2015; Kim 2014). Unfortunately, no designated lower level of the QTc interval is completely safe from arrhythmic risk.

Oral Targeted Chemotherapy Agents Involved

Table 1-8 lists the oral targeted chemotherapy agents that have been associated with QTc prolongation. Also listed is the recommended ECG monitoring included in the prescribing information of each agent.

Other Risk Factors

Other situations or conditions may add to the risk of QTc prolongation. Most TdP cases occur in women because of the inherently longer QTc interval and greater prolongations when women are exposed to QTc-prolonging medications. In addition, electrolyte concentrations (potassium, magnesium, calcium) in the low to low-normal ranges have been identified in about 40% of TdP cases. Unfortunately, many patients with cancer have low/fluctuating electrolyte concentrations, especially when diarrhea and vomiting occur with antineoplastic agents. Box 1-7 lists other factors associated with the risk of QTc prolongation.

One of the greatest risk factors for developing QTc prolongation is receiving concurrent medications that prolong the QTc interval. These drugs may prolong depolarization, reduce

Table 1-8. Oral Targeted Chemotherapy Agents Associated with QTc Prolongation and Indications for ECG Monitoring

Drug	FDA Label-Approved Indications	QTc Prolongation Frequency	Recommended ECG Monitoring
Crizotinib	NSCLC	++ (grade 3/4 ++)	For high-risk patients
Dasatinib	CML, Ph^+ ALL	+	For high-risk patients
Lapatinib	Breast cancer	+	For high-risk patients
Lenvatinib	Thyroid cancer	++9% (grade 3/4 ++%)	For high-risk patients
Nilotinib	CML	++	At baseline, at 7 days after initiation or dose change, and periodically thereafter
Osimertinib	NSCLC	++	For high-risk patients
Pazopanib	Kidney cancer, soft tissue sarcoma	++	At baseline and periodically thereafter
Sorafenib	Liver cancer, kidney cancer, thyroid cancer	+	No specific recommendations
Sunitinib	GIST, kidney cancer, pancreatic neuroendocrine cancer	+	At baseline and periodically thereafter
Vandetanib	Thyroid cancer	++ (grade 3/4 ++)	At baseline, at 2–4 wk, at 8–12 wk, and every 3 mo thereafter (for initiation and any dose reduction for QTc prolongation)
Vemurafenib	Melanoma	++	At baseline and 15 days after initiation; then monthly x 3; then every 3 mo thereafter

Information from: UpToDate, Micromedex, package inserts, and literature sources.

repolarization, or both. Box 1-8 lists some nononcologic medications associated with QTc prolongation that patients with cancer may be receiving. Additive prolongation of the QTc interval with several drugs increases the risk of adverse outcomes.

Drug Interactions Involved in QTc Prolongation Risk

Because high medication blood concentrations increase the risk of significant QTc prolongation, drug interactions that increase blood concentrations should be expected to have a substantial effect. Most oral targeted cancer treatments are metabolized by the CYP3A4 enzyme system. Strong and moderate CYP3A4 inhibitors can increase the blood concentrations of the oral cancer treatments and lead to greater QTc prolongation. It is crucial to conduct a thorough medication list screening to identify potential drug interactions (van Leeuwen 2014).

Other pharmacokinetic interactions that affect oral cancer treatment blood concentrations may be involved. Special attention should be paid to the administration recommendations for each oral targeted cancer treatment. For example, with nilotinib and pazopanib, administration with a high-fat meal can increase the bioavailability and serum concentrations; these medications should be taken on an empty stomach.

Assessment

Box 1-9 shows the oncology grading criteria for QTc prolongation with cancer treatments.

Monitoring and Risk Management

For patients receiving QTc-prolonging cancer treatments, a thorough assessment of risk factors should be completed and the risks minimized, if possible.

Box 1-7. Risk Factors for QTc Prolongation

- Female sex
- Age > 65 yr
- Electrolyte abnormalities: Hypokalemia, hypomagnesemia, hypocalcemia
- Diuretic use (leading to lower intracellular electrolyte concentrations)
- Cardiac conditions: Bradycardia, bundle branch block, heart failure, previous myocardial infarction, conversion from atrial fibrillation, mitral valve prolapse, atrioventricular block
- Congenital long QT syndrome, prolonged QT interval at baseline
- Endocrine conditions: Hypothyroidism, hyperparathyroidism, hyperaldosteronism, pheochromocytoma
- High dosage, high blood concentrations, or rapid infusion of QTc-prolonging medications
- Medications that slow atrioventricular node conduction: β-Blockers, digoxin, diltiazem, verapamil

Information from: Li EC, Esterly JS, Pohl S, et al. Drug-induced QT-interval prolongation: considerations for clinicians. Pharmacotherapy 2010;30:684-701; and Locatelli M, Criscitiello C, Esposito A, et al. QTc prolongation induced by targeted biotherapies used in clinical practice and under investigation: a comprehensive review. Targ Oncol 2015;10:27-43.

Monitoring the ECG for QTc prolongation is warranted for high-risk oral cancer treatments (see Table 1-8). More frequent monitoring is recommended for patients at high risk and those with identified drug interactions or concomitant QTc-prolonging medications. In these situations, it is prudent to check the ECG at baseline, within 1 week after initiating the cancer treatment, and then monthly thereafter.

Electrolyte concentrations should also be monitored routinely. Potassium, magnesium, and calcium supplements should be given to raise blood concentrations to normal (high-normal in patients at high risk, especially those taking diuretics).

For patients receiving concomitant medications that prolong the QTc or CYP3A4 inhibitors, alternative medications should be considered. However, for some conditions such as depression, alternative treatments may not be ideal because of either less efficacy or greater adverse effects. When possible, use lower doses, and avoid intravenous administration of concomitant medications that prolong the QTc interval (Locatelli 2015; van Leeuwen 2014; Nachimuthu 2012; Al-Khatib 2003; Crouch 2003).

There are no standard guidelines regarding when to interrupt/dose reduce/discontinue the antineoplastic agent according to the degree to which the QTc is prolonged (Curigliano 2016; Locatelli 2015). The cancers for which the oral targeted treatments are recommended are usually life threatening, and a risk-benefit consideration is required. In general, the treatment is not altered for grade 1 or grade 2 prolongations. For grade 3 reactions, reversible risk factors should be attended to (electrolyte concentrations, concomitant medications), and treatment interruption should be considered. For grade 4 QT prolongation, the anticancer treatment should be discontinued; if the QTc level cannot be lowered, rechallenge would be extremely risky, and the oncologist should consider other cancer treatments.

Box 1-8. Nononcologic Drugs Associated with QTc Prolongation

Cardiac medications
- Ibutilide, sotalol, dofetilide, amiodarone, dronedarone, ranolazine

Pain medications
- Methadone

Anti-infective medications
- Macrolides, fluoroquinolones, azole antifungals, pentamidine

Antipsychotic medications
- Chlorpromazine, haloperidol, quetiapine, risperidone, ziprasidone

Antiemetics
- Ondansetron, granisetron, dolasetron, droperidol, metoclopramide, prochlorperazine

Antidepressants
- Citalopram, fluoxetine, escitalopram, sertraline, venlafaxine, trazodone

Box 1-9. QT Prolongation NCI CTCAE Grading Criteria

Grade 1
- QTc 450–480 msec

Grade 2
- QTc 481–500 msec

Grade 3
- QTc ≥ 501 msec on at least two separate ECGs

Grade 4
- QTc ≥ 501 msec or > 60 msec change from baseline AND torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

Grade 5
- Death

msec = milliseconds.

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

Patient Care Scenario

R.H. is a 67-year-old man (height 71 inches, weight 91 kg) with recently diagnosed kidney cancer with metastatic disease found in his bones. His medical history includes type 2 diabetes, gout, depression, and HTN. In addition, R.H. has coronary artery disease and has had an ST-segment elevation myocardial infarction. His home drugs include metformin extended release 1000 mg twice daily, atorvastatin 40 mg daily, allopurinol 300 mg daily, metoprolol succinate 25 mg twice daily, hydrochlorothiazide 25 mg daily, aspirin 81 mg daily, citalopram 20 mg daily, and ibuprofen 600 mg as needed. He is not taking lisinopril 10 mg, which was prescribed for him, but he does not know why. His blood pressure today is 155/93 mm Hg, and his heart rate is 76 beats/minute. Laboratory tests today include BUN 23 mg/dL, SCr 1.38 mg/dL, and K 3.2 mEq/L, and his liver function tests are within normal ranges. His oncologist prescribed pazopanib 800 mg (4 x 200-mg capsules) daily because it is an approved first-line treatment for kidney cancer and is better tolerated than alternatives. What additional baseline testing should be done for R.H.? What would be the best monitoring plan to address the potential cardiovascular adverse effects of pazopanib? Recommend any appropriate medication changes.

ANSWER

This patient is at risk of worsening of HTN, as well as LVD/HF and QTc prolongation with pazopanib. For the HTN, it would be best to examine his blood pressure record and home blood pressure monitoring to understand whether today's elevated reading is because of acute stress of the oncologist visit or because his blood pressure is usually elevated. It is important to discover why he is not taking lisinopril because ACE inhibitors are an important medication class, not only for controlling HTN associated with pazopanib but also for coronary artery disease and diabetes. Because he had a myocardial infarction in the past, he is at high risk of LVD/HF with pazopanib. For patients at high risk, LVEF should be assessed at baseline and periodically while taking pazopanib. In addition, he is at risk of QTc prolongation with both pazopanib and citalopram. The baseline testing should include additional blood pressure readings, LVEF assessment, ECG, and full electrolyte panel. The test results were blood pressures of 146–158 mm Hg systolic and 91–17 mm Hg diastolic with a heart rate of 60–75 beats/minute. It is important to achieve his goal blood pressure of less than 140/90 mm Hg before initiating pazopanib. It turns out that the patient's lisinopril was held during a hospitalization 3 weeks ago, but he did not understand the instructions to restart it on discharge. His LVEF is 54%, which is adequate to initiate pazopanib. The QTc interval on ECG is 425 milliseconds, which is adequate to initiate pazopanib. However, checking the magnesium and calcium concentrations as well as the potassium concentration is needed, especially because he is taking a diuretic. The ideal monitoring plan for this patient would be (1) blood pressure readings daily at home (called in to the clinic) and/or weekly measurements in the clinic; (2) LVEF assessment periodically during pazopanib therapy, although specific recommendations for the interval are not available; (3) periodic ECG testing for QTc prolongation during therapy, ideally about 1–2 weeks after initiating pazopanib (he is at a higher risk because of concomitant medication and hypokalemia), and then monthly.

Recommended initial medication changes should include:

(1) Reinitiate lisinopril, and recheck renal function and potassium concentration 1–2 weeks later.

(2) Consider increasing the metoprolol dose or adding either amlodipine or felodipine if reinitiating lisinopril is inadequate to maintain blood pressure less than 140 mm Hg.

(3) Supplement potassium to maintain potassium concentrations in the normal range.

(4) Consider changing the antidepressant to an agent without a high risk of QTc prolongation. However, most of the effective antidepressants can increase QTc intervals, and changing antidepressants is not always successful and places patients at risk of recurrent depression.

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METABOLIC ADVERSE EFFECTS FROM ORAL TARGETED CHEMOTHERAPY

Hypothyroidism

Pharmacology and Mechanism of Toxicity

Among the endocrine toxicities of oral targeted cancer treatments, thyroid disorders may be the most common. Although hyperthyroidism has been reported with a few agents, hypothyroidism (HoT) is more commonly recognized. Different mechanisms for HoT development have been identified. With VSP inhibitors, the likely mechanism is related to capillary regression in the thyroid gland (Fallahi 2014; Illouz 2014; Ahmadieh 2013). In this scenario, transient hyperthyroidism may occur before HoT develops, which may be associated with thyroid autoantibody development. With other agents such as imatinib, the metabolism/elimination and transport of tetraiodothyronine seem to be altered.

The onset of HoT can be as early as the first cycle of oral targeted cancer agents, though the cumulative incidence seems to increase with prolonged treatment. For some patients, HoT resolves after discontinuing the cancer treatment, and for others, HoT persists. For agents such as sunitinib, which can be given in a cyclical schedule, the thyroid-stimulating hormone (TSH) concentrations may rise and fall during the cycle.

The symptoms of HoT are somewhat vague and nonspecific. They include adverse effects that can also be attributed to cancer or other cancer treatment such as alopecia, paresthesias, lethargy, depression, difficulty concentrating, cognitive decline, weakness, myalgias/arthralgias, decreased exercise tolerance, anorexia, and constipation. Symptoms are also related to the duration and severity of HoT and the rapidity of its development. Untreated HoT can also lead to HTN and hyperlipidemia, which can also be adverse effects of oral targeted cancer treatments (Rugge 2015; Gaitonde 2012).

Oral Targeted Chemotherapy Agents Involved

Table 1-9 lists the oral targeted cancer treatments associated with HoT. The incidence of HoT identified in clinical trials can vary widely, depending on which measure of HoT is used (e.g., TSH greater than the upper limit of normal, TSH greater than twice the upper limit of normal, dose adjustment of levothyroxine).

Assessment and Monitoring Plans

Box 1-10 shows the oncology-related grading criteria for HoT. However, this is not valuable in making treatment decisions. The standard HoT descriptions and categorizations apply to patients with cancer as well, as seen in Table 1-10 (Jonklaas 2014; Gaitonde 2012).

With the wide variation in the time to onset and severity of HoT, routine monitoring of thyroid function tests is recommended with the oral targeted cancer treatments listed in Table 1-9. There are no consensus- or evidence-based

Table 1-9. Oral Targeted Chemotherapy Agents Associated with Hypothyroidism

Drug	FDA Label-Approved Indications	Regimen Schedule	Frequency
Axitinib	Kidney cancer	Continuous	++ to +++++
Cabozantinib	Thyroid cancer, kidney cancer	Continuous	++ to +++++
Dasatinib	Ph^+ ALL, CML	Continuous	+ to ++++
Imatinib	Ph^+ ALL, CML, GIST	Continuous	+ to +++
Nilotinib	CML	Continuous	+ to +++
Pazopanib	Kidney cancer, soft tissue sarcoma	Continuous	
Sorafenib	Liver cancer, kidney cancer, thyroid cancer	Continuous	++ to ++++
Sunitinib	GIST, kidney cancer, pancreatic neuroendocrine cancer	Continuous OR 4 wk on, then 2 wk off OR 2 wk on, then 1 wk off	++ to +++++
Vandetanib	Thyroid cancer	Continuous	++ to +++++

Information from: UpToDate, Micromedex, package inserts, and literature sources.

Box 1-10. NCI CTCAE Hypothyroidism Grading Criteria

Grade 1
- Asymptomatic; clinical or diagnostic observations only; intervention not indicated

Grade 2
- Symptomatic; thyroid replacement indicated; limiting instrumental ADLs

Grade 3
- Severe symptoms; limiting self-care ADLs; hospitalization indicated

Grade 4
- Life-threatening consequences; urgent intervention indicated

Grade 5
- Death

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

recommendations regarding the frequency of thyroid function evaluations. Sunitinib can be given in a lower continuous dosing or in a higher cycled regimen (e.g., 4 weeks on, then 2 weeks off), depending on the cancer being treated and the patient's tolerance of other adverse effects. For the cycled regimen of sunitinib, it has been suggested that the thyroid function tests be evaluated at baseline and at the beginning and end of each "on" period. For the continuously administered agents, a reasonable approach is to monitor laboratory tests at baseline and then every 1–2 months for the first 4 months, then periodically. Thyroid function tests should continue to be monitored every 1–2 months in patients who need thyroid hormone replacement because their requirements may change over time with continued cancer treatment (Fallahi 2014; Illouz 2014; Ahmadieh 2013).

In addition, some of these agents are approved for the treatment of thyroid cancer, and most of these patients will have already undergone surgical removal or ablation of the thyroid gland and are already taking thyroid hormone replacement. Patients with preexisting HoT should also be monitored closely because their thyroid hormone replacement needs may change.

Treatment Recommendations

Treatment recommendations for cancer treatment–induced HoT have not been established. There is no evidence that HoT in patients with cancer should be treated any differently from HoT in patients without cancer. The treatment goals are to minimize HoT-related symptoms and the effect of HoT on the lipid profile and cardiovascular disease (which can also be negatively affected by oral targeted cancer treatments). Table 1-11 shows standard levothyroxine dosage recommendations for patients who do not have cancer (Jonklaas 2014; Gaitonde 2012). There are no published dosage recommendations specific to people with cancer; however, most patients will be older than 50–60 years.

It is important to avoid overtreatment with levothyroxine, which can worsen atrial fibrillation and osteoporosis. For patients with cancer who lose a substantial amount of weight and lean body mass, the levothyroxine needs may change.

Hyperglycemia

Pharmacology and Mechanism of Toxicity

As seen in Table 1-12, several oral targeted cancer treatments are associated with hyperglycemia (HG). These medications

Table 1-10. Evaluation of Thyroid Function Tests

Laboratory Tests		Recommendation
TSH (mIU/L)	Tetraiodothyronine (ng/dL)	
Low (< 0.4)		Consider hyperthyroid state and further evaluation
Normal (0.4–4.0)		Euthyroid
High (> 10.0)	Low (< 0.76)	Overt/primary HoT; treatment is indicated
Slightly high (4.0–10.0)	Normal (0.76–1.46)	Subclinical HoT; treatment may be indicated, but should be based on clinical judgment; evidence has not established a clear-cut benefit

HoT = hypothyroidism; TSH = thyroid-stimulating hormone.

Information from: Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. Thyroid 2014;24:1670-728; Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician 2012;86:244-51; and Rugge JB, Bougatsos C, Chou R. Screening and treatment of thyroid dysfunction: an evidence review for the US Preventive Services Task Force. Ann Intern Med 2015;162:35-45.

Table 1-11. Standard Levothyroxine Dosage Recommendations

Patient Population	Regimen
Healthy younger people	Start at full replacement dose of 1.6 mcg/kg of lean body mass daily
Older people Those with cardiovascular disease Those with subclinical HoT	Start at 25–50 mcg daily, and titrate slowly by 12.5- to 25-mcg increments, guided by TSH concentrations

Information from: Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism. Thyroid 2014;24:1670-728; and Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. Am Fam Physician 2012;86:244-51.

Table 1-12. Oral Targeted Chemotherapy Agents Associated with Hyperglycemia

Drug	FDA Label-Approved Indications	Regimen Schedule	Frequency
Alectinib	NSCLC	Continuous	++++
Axitinib	Kidney cancer	Continuous	++++
Bexarotene	Cutaneous T-cell lymphoma, mycosis fungoides	Continuous	++
Ceritinib	NSCLC	Continuous	++++
Dabrafenib	Melanoma	Continuous	++++
Everolimus	Kidney cancer, breast cancer, pancreatic neuroendocrine cancer	Continuous	+++ to +++++
Imatinib	CML, Ph^+ ALL, GIST	Continuous	++
Lenalidomide	Multiple myeloma, mantle cell lymphoma, myelodysplastic syndrome	Continuous OR 3 wk on, then 1 wk off	++ to +++
Nilotinib	CML	Continuous	++++
Olaparib	Ovarian cancer	Continuous	++
Panobinostat	Multiple myeloma	2 wk on, then 1 wk off	++
Pazopanib	Kidney cancer, sarcoma	Continuous	++++
Pomalidomide	Myeloma	3 wk on, then 1 wk off	+++
Ponatinib	CML	Continuous	+++++
Sonidegib	Basal cell skin cancer	Continuous	+++++
Sunitinib	Kidney cancer, GIST, pancreatic neuroendocrine cancer	Continuous OR 2 wk on, then 1 wk off OR 4 wk on, then 2 wk off	+++
Trametinib	Melanoma	Continuous	+++++
Vandetanib	Thyroid cancer	Continuous	++
Vorinostat	Cutaneous T-cell lymphoma	Continuous	++ to +++++

Information from: UpToDate, Micromedex, package inserts, and literature sources.

represent several different classes, different targets and mechanisms of action, and different indications. For most of these agents, the mechanism by which HG arises has not been identified. However, for everolimus, the mechanism of action directly relates to the development of HG.

Everolimus is an mTOR inhibitor, as is sirolimus and tacrolimus used in transplant immunosuppression. The HG seen with mTOR inhibitors is a class effect, related to the downstream effects of the mTOR pathway, which includes elements of the insulin signaling mechanism. Inhibition of the pathway leads to both impaired insulin secretion and a reduction in insulin sensitivity/promotion of insulin resistance (Vergès 2015; Aapro 2014; Vergès 2014; Busaidy 2012).

There is a significant overlap between patients with cancer and patients with diabetes or prediabetes. Unfortunately, in many patients, diabetes is not diagnosed until patients present for cancer treatment. Patients with both cancer and diabetes have higher rates of infections, chemotherapy toxicity, and cancer mortality (Busaidy 2012; Vigneri 2009). Unfortunately, patients with diabetes are often excluded from clinical trials with some anticancer medications.

In addition, corticosteroids are widely prescribed for several different reasons in cancer treatment (Box 1-11). Oral targeted cancer agents may be used concurrently with intravenous/oral chemotherapy and immunological agents, which require the use of corticosteroids. The HG with corticosteroids largely occurs in the postprandial phase and may resolve overnight.

Oral Targeted Chemotherapy Agents Involved

See Table 1-12 for oral targeted cancer treatments associated with HG.

Assessment, Monitoring Plans, and Appropriate Treatment Goals

There are no standard guidelines for monitoring HG with most of these oral targeted treatments. Given that many patients treated with these agents have previously undiagnosed diabetes, it is important that fasting blood glucose (FBG) and A1C be assessed at baseline because the treatment of HG in these patients may be different from that in patients without preexisting diabetes.

Box 1-11. Indications for Corticosteroids in Cancer Treatment

- Appetite stimulation
- Brain and spinal cord metastases
- Cancer-related fatigue
- Chemotherapy regimens for lymphoid cancers
- Hypersensitivity/allergic reaction to chemotherapy agents
- Nausea and vomiting

For patients treated with everolimus, it is recommended that monitoring be based on baseline glucose concentrations (Vergès 2015; Vergès 2014). For normoglycemic patients, the FBG should be checked every 2 weeks during the first month or two of treatment and then monthly, together with A1C every 3 months. For those with prediabetes or metabolic syndrome, the recommendations call for self-monitored blood glucose (SMBG) checking once daily before breakfast. For patients with preexisting diabetes, frequent (two to four times daily) SMBG is called for. In patients prescribed one of the other agents in Table 1-12, it is recommended to check SMBG every 2 weeks during the first month or two, then monthly.

Appropriate treatment goals for those who develop new or worsening HG depend on the life expectancy and comorbidities of the individual patient. These oral targeted cancer treatments are used in patients with a fairly long cancer-related life expectancy as well as those with metastatic disease and a limited life expectancy. Estimating the life expectancy of an individual with cancer is extremely difficult, but a conversation with the oncologist may determine whether it should be measured in months versus years. In all patients, the treatment goals include preventing/resolving the acute and subacute toxicities of HG such as polyuria, polydipsia, infections, hypercoagulability, weight loss, and osmotic diuresis (Goldman 2016; Busaidy 2012). However, strict glucose control would be inappropriate in those with poor appetite, erratic food intake, nausea, or diarrhea. One set of recommendations for the management of HG in patients receiving cancer treatment calls for treatment goals of FBG less than 160 mg/dL, all random glucose concentrations less than 200 mg/dL, and an A1C of 8% or less (Goldman 2016; Busaidy 2012). Box 1-12 shows the oncologic grading criteria for treatment-related HG.

Treatment Recommendations

Therapeutic lifestyle choices for diabetes may not be appropriate for all patients with cancer. Many patients with cancer struggle with poor oral intake, taste disturbances, anorexia,

Box 1-12. NCI CTCAE Hyperglycemia Grading Criteria

Grade 1
- FBG 110–160 mg/dL

Grade 2
- FBG 161–250 mg/dL

Grade 3
- 251–500 mg/dL; hospitalization indicated

Grade 4
- > 500 mg/dL; life-threatening consequences

Grade 5
- Death

FBG = fasting blood glucose.

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

and cancer-related fatigue. Asking the patient to follow a diet low in carbohydrates can reduce the amount of food the patient is willing and able to eat. Advising the patient to exercise, although helpful for combating fatigue, may be met with difficulty by patients with significant pain or bone metastases (Berger 2016).

For patients with previously undiagnosed diabetes and an elevated A1C before starting cancer treatment, it is appropriate to initiate metformin (Vergès 2015; Vergès 2014; Busaidy 2012). Many of these patients can have variable and reduced renal function, and metformin should be held if the GFR falls below 30 mL/minute/1.73 m^2. In addition, many patients with cancer have frequent imaging scans requiring iodinated contrast, and metformin should be held for 48 hours after administration of contrast. Patients with preexisting diabetes should continue on their current treatment until it is determined whether their glucose control has worsened.

There are no standard treatment guidelines for HG associated with all oral targeted cancer treatment, although recommendations exist for those treated with everolimus (Busaidy 2012). It also would be appropriate to rely on the standard diabetes treatment algorithms, with some additional considerations (Chamberlain 2016). Noninsulin diabetes treatments with a moderate to high risk of hypoglycemia should be avoided in patients with nausea, poor/variable oral intake, or significant diarrhea. Although it adds substantial complexity, insulin treatment is not uncommonly used in patients with cancer. It offers greater flexibility (especially in patients with erratic oral intake) and speed in correcting HG. In appropriate patients, mealtime short-acting insulin with/without basal insulin may be a good treatment choice (Goldman 2016; Busaidy 2012).

Of note, although with interruption or discontinuation of the cancer treatment, the HG may resolve in some cases, it may persist in others. It is important to adjust the hyperglycemic treatment appropriately in these situations. In addition, some of the agents listed in Table 1-12 are given cyclically, instead of continuously; thus, the effect on glucose concentrations may vary according to the dosage schedule.

Hyperlipidemia

Pharmacology and Mechanism of Toxicity

Some oral targeted cancer treatments are associated with hyperlipidemia. In some cases, this can develop quite quickly, within the first 2 weeks of therapy, but in other cases, it can develop more slowly. For most of these agents, the mechanism of toxicity is unknown. For everolimus, an mTOR inhibitor, the mechanism is related to mTOR's role in lipid metabolism. Hyperlipidemia is more likely because of reduced peripheral lipid clearance than because of increased lipid production (Vergès 2014; Busaidy 2012).

Oral Targeted Chemotherapy Agents Involved

Table 1-13 describes the oral targeted cancer treatments associated with hyperlipidemia.

Assessment and Monitoring Plans

With everolimus treatment, it is recommended to check a fasting lipid panel (FLP) at baseline and then every month or cycle of cancer treatment (Busaidy 2012). With bexarotene treatment, it is recommended to check an FLP at baseline and

Table 1-13. Oral Targeted Chemotherapy Agents Associated with Hyperlipidemia

Agent	FDA Label-Approved Indications	Hypercholesterolemia Incidence	Hypertriglyceridemia Incidence	Recommended FLP Monitoring
Bexarotene	Cutaneous T-cell lymphoma, mycosis fungoides	++++ to +++++	+++++	Baseline, then weekly until stabilized, then every 2 mo
Everolimus	Kidney cancer, breast cancer, pancreatic neuroendocrine cancer	+++ to +++++	+++ to +++++	Baseline and every 1 mo
Lenvatinib	Thyroid cancer	++	NR	Baseline and every 2 mo
Nilotinib	CML	+++	++	Baseline and every 2 mo
Ruxolitinib	Myelofibrosis, polycythemia vera	+++ to ++++	++	Baseline and every 2 mo
Tretinoin	Acute promyelocytic leukemia	++++ to +++++	++++ to +++++	At 2–3 mo of treatment

FLP = fasting lipid panel.

Information from: UpToDate, Micromedex, package inserts, and literature sources.

Box 1-13. NCI CTCAE Hyperlipidemia Grading Criteria

Hypercholesterolemia

Grade 1
- 200–300 mg/dL

Grade 2
- 301–400 mg/dL

Grade 3
- 401-500 mg/dL

Grade 4
- >500 mg/dL

Hypertriglyceridemia

Grade 1
- 150–300 mg/dL

Grade 2
- 301–500 mg/dL

Grade 3
- 501–1000 mg/dL

Grade 4
- > 1000 mg/dL

Grade 5
- Death

Information from: DHHS. Common Terminology Criteria for Adverse Events. 2016.

then every week until lipids stabilize and every 2 months. For tretinoin therapy, an FLP should be checked after 2–3 months of treatment. For the other agents listed in Table 1-13, no specific recommendations are available, but it would be reasonable to check an FLP at baseline and every 2 months.

The oncology grading criteria for hyperlipidemia are shown in Box 1-13.

Appropriate Treatment Goals and Treatment Recommendations

Therapeutic lifestyle choices for hyperlipidemia may not be feasible for all patients with cancer. Many patients struggle to maintain adequate protein intake, and advising patients to follow a low-fat diet may further reduce their protein intake. Like patients with HG, patients with significant pain or bone metastases often have difficulty exercising.

Most of the available treatment recommendations for treatment-related hyperlipidemia predate the new hyperlipidemia treatment guidelines. Similar to treatment of hyperglycemia, the appropriate treatment goals for hyperlipidemia depend to some extent on the patient's projected life expectancy. If the patient's life is likely to be measured in many years, it is reasonable to think the patient will benefit from the cardiovascular risk reduction of hyperlipidemia treatment. These patients should be treated according to the general hyperlipidemia treatment guidelines (Jacobson 2015a; Jacobson 2015b; Stone 2014). For patients with a life expectancy of 1 year or more, treatment should be undertaken if LDL is more than 190 mg/dL or TG are greater than 300 mg/dL. Even for patients with a short life expectancy measured in months, treatment for TG greater than 500 mg/dL is indicated to reduce the incidence of acute pancreatitis (Busaidy 2012).

It is crucial to screen for drug interactions between these agents and lipid-lowering treatments. There are several reported drug interactions between these agents and statins, gemfibrozil, and fenofibrate. In most cases, alternative statins or fibrates can be identified.

Practice Points

Treating adverse effects with oral targeted cancer treatments is crucial to enabling a patient to stay on potentially lifesaving cancer treatments. Monitoring for and managing these adverse effects requires collaboration between primary care practitioners and the oncology care team.

- **Acneiform papulopustular rash is treated with anti-inflammatory agents such as topical hydrocortisone and clindamycin, systemic doxycycline or tetracycline, and potentially oral corticosteroids.**
- **Treatment of HFSR includes urea-based creams and topical corticosteroids and may require holding the cancer treatment and potentially reinitiating it at a lower dose.**
- **The photosensitivity that occurs with vemurafenib is primarily related to UVA exposure; sunscreens should include ingredients that block UVA.**
- **HTN commonly occurs with VSP inhibitors; appropriate monitoring and treatment is essential, usually starting with an ACE inhibitor or a dihydropyridine calcium channel blocker.**
- **LVEF should be evaluated in patients receiving select oral targeted cancer treatments. Treatment of LVD/HF in patients with cancer is similar to that of patients without cancer.**
- **Several agents can increase the QTc interval. Management strategies include ECG and electrolyte monitoring and consideration of changes in concomitant medications.**
- **Treatment of cancer therapy–induced HoT is consistent with the usual treatment of HoT.**
- **For patients who develop HG or hyperlipidemia, the predicted life expectancy should be considered before determining the appropriate treatment goals. If treatment is warranted, usual therapy is appropriate, with consideration given to drug interactions.**

CONCLUSION

Dermatologic, cardiovascular, and endocrine toxicities of oral targeted cancer treatments require careful monitoring, adequate treatment, and possible dose adjustments. Optimal patient care requires collaboration between the patient's primary care providers and the oncologists. Pharmacists in any setting can play an important role in the monitoring and treatment of these toxicities. Careful management of these adverse effects will allow the patient to gain the maximal benefit of the cancer treatment.

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Self-Assessment Questions

Questions 1–4 pertain to the following case.

K.S., a 72-year-old man (height 67 inches, weight 108 kg), has advanced liver cancer and will be initiated on sorafenib 400 mg orally twice daily. His medical history includes alcoholism (now sober), hepatic cirrhosis with ascites and hypertension (HTN), and coronary artery disease (after stent placement 4 years ago). K.S.'s current drugs include aspirin 81 mg daily, lisinopril 20 mg daily, metoprolol succinate 100 mg daily, and atorvastatin 40 mg daily.

1. In counseling K.S. on hand-foot skin reaction (HFSR), which one of the following is most important to include?

   A. Folliculitis
   B. Hyperkeratosis
   C. Erythema of sun-exposed skin
   D. Alopecia

2. Which of the following is the best recommendation to prevent HFSR in K.S.?

   A. Topical urea-based cream and avoidance of skin friction
   B. Topical clobetasol and oral gabapentin
   C. Topical clindamycin and topical hydrocortisone
   D. Oral doxycycline and sunscreen

3. K.S. develops overt HoT. Which one of the following levothyroxine daily dosages is best to recommend for K.S.?

   A. 25 mcg
   B. 75 mcg
   C. 100 mcg
   D. 175 mcg

Questions 4–7 pertain to the following case.

M.K. is a 47-year-old man with new diagnosis of metastatic kidney cancer. He had surgery 6 weeks ago to remove the cancerous kidney and relieve his hematuria. M.K. has HTN (controlled with amlodipine 10 mg daily) and HoT (controlled with levothyroxine 150 mcg daily.) His oncologist has prescribed sunitinib 50 mg daily for 4 weeks on, then 2 weeks off (then repeat). The oncologist estimates that M.K.'s life expectancy is 1–2 years.

4. Which one of the following left ventricular dysfunction (LVD)/heart failure (HF) monitoring plans is most appropriate for M.K.?

   A. No routine monitoring for left ventricular ejection fraction (LVEF) is required.
   B. Assess LVEF before therapy initiation, 1 month after, and every 3 months thereafter. Also assess LVEF at 2, 4, 10, and 16 weeks and then as clinically indicated after dose reduction or treatment interruption.
   C. Baseline and periodic LVEF are recommended.
   D. Assess LVEF before therapy initiation, at 1 month, and then at 2- to 3-month intervals while on therapy.

5. M.K. lives far from the clinic. He has been checking his blood pressure at home three or four times per week and readings have mainly been 145–167 mm Hg/85–105 mm Hg. Which one of the following is best to recommend for M.K.?

   A. Make no change in HTN treatment.
   B. Increase the amlodipine dose.
   C. Start lisinopril and recheck basic metabolic panel (BMP) in 1–2 weeks.
   D. Start diltiazem and check BMP in 4 weeks.

6. After 2 weeks of sorafenib therapy, M.K. develops grade 2 HFSR. Which one of the following is best to recommend for M.K.?

   A. Give urea-based cream 10% topically twice daily.
   B. Give clobetasol 0.05% topically once or twice daily plus urea-based cream 20% twice daily.
   C. Give minocycline orally 100 mg daily.
   D. Discontinue sorafenib permanently.

7. After 6 weeks of sorafenib therapy, M.K.'s thyroid function tests are repeated; TSH is 15 mIU/L, and tetraiodothyronine is 0.3 ng/dL. Which one of the following is best to recommend for M.K.?

   A. Make no change at this time.
   B. Increase levothyroxine to 200 mcg daily.
   C. Increase levothyroxine to 175 mcg daily.
   D. Decrease levothyroxine to 125 mcg daily.

Questions 8–10 pertain to the following case.

G.F. is a 73-year-old woman with a diagnosis of epidermal growth factor receptor (EGFR) mutation–positive non–small cell lung cancer. She will be treated with afatinib 40 mg daily. G.F. was previously treated with erlotinib and developed grade 2 EGFR papulopustular eruptions.

8. G.F. makes an appointment to discuss the adverse effects related to her skin. Which one of the following is most important to counsel G.F. to monitor for?

   A. Hyperkeratosis
   B. Involvement of the feet
   C. Blister formation
   D. Involvement of the face

9. Which one of the following is best to recommend for prophylaxis of papulopustular eruptions in G.F.?

   A. Give hydrocortisone topically and doxycycline orally.
   B. Give urea-based cream topically.

C. Give clobetasol topically and minocycline orally.
D. No prophylaxis is recommended.

10. G.F. declines prophylaxis but then develops grade 1 papulopustular eruptions on the face. Which one of the following is best to recommend for G.F.?

    A. Clindamycin topically and clobetasol topically
    B. Clindamycin topically and minocycline orally
    C. Minocycline orally and corticosteroids orally
    D. Hydrocortisone topically and clindamycin topically

Questions 11–13 pertain to the following case.

E.M. is a 33-year-old woman with metastatic melanoma. She will be initiated on concurrent vemurafenib and cobimetinib. E.M. has no significant comorbidities. Her home drugs include citalopram, fexofenadine, and fluticasone nasal spray.

11. Which one of the following adverse effects is most important to monitor for in E.M.?

    A. HTN and papulopustular eruption
    B. LVD/HF and QTc prolongation
    C. HoT and HFSR
    D. Hyperglycemia (HG) and HTN

12. Which one of the following products would be best to recommend for UVA sun protection for E.M.?

    A. Titanium dioxide and oxybenzone
    B. Para-aminobenzoic acid and zinc oxide
    C. Padimate O and cinoxate
    D. Avobenzone and octinoxate

13. Which one of the following other nonpharmacologic preventive techniques is best to recommend for E.M.?

    A. Wash skin with non-detergent cleanser.
    B. Avoid friction on the skin.
    C. Avoid swimming.
    D. Place window screens in the car.

Questions 14–16 pertain to the following case.

F.G. is a 60-year-old man with newly diagnosed chronic myeloid leukemia. His oncologist has prescribed nilotinib 400 mg twice daily.

14. Which one of the following is best to recommend as regards ECG monitoring for QTc interval in F.G.?

    A. Regardless of risk: monitor at baseline, at 7 days after initiation or dose change, and periodically thereafter.
    B. Only if he is at high risk: monitor at baseline and periodically thereafter.
    C. Regardless of risk: monitor at baseline, at 15 days after initiation, then monthly x 3, then every 3 months thereafter.
    D. Only if he is at high risk: monitor at baseline, at 2–4 weeks, and at 8–12 weeks and every 3 months thereafter (for initiation and any dose reduction for QTc prolongation).

15. Which one of the following characteristics, if present in F.G., would most increase his risk of QTc prolongation?

    A. Male sex
    B. Diabetes
    C. Hypokalemia
    D. HTN

16. Which one of the following drugs, if prescribed for F.G., would be most likely to increase the risk of QTc prolongation with nilotinib?

    A. Oxycodone
    B. Fluconazole
    C. Pantoprazole
    D. Bupropion

Questions 17–19 pertain to the following case.

J.P. is a 63-year-old woman with metastatic breast cancer. After trials of several other types of chemotherapy, the oncologist wants to initiate J.P. on everolimus and exemestane. The oncologist estimates that J.P.'s life expectancy is measured in months rather than years. Her medical history includes diabetes (treated with metformin and insulin glargine) and HTN (treated with amlodipine and hydrochlorothiazide).

17. If J.P. develops HG related to everolimus, which one of the following would be the most appropriate set of treatment goals?

    A. A1C less than 7%; fasting blood glucose (FBG) less than 160 mg/dL
    B. A1C less than 8%; FBG less than 200 mg/dL
    C. A1C less than 7%; FBG less than 110 mg/dL
    D. A1C less than 8%; FBG less than 160 mg/dL

18. After she is initiated on everolimus, which one of the following is the best schedule for fasting lipid panels to monitor for hyperlipidemia in J.P.?

    A. At baseline, then monthly
    B. Weekly until stabilized
    C. After 2–3 months
    D. Every 2 weeks

19. J.P. develops hyperlipidemia. Which one of the following treatment goals is best to recommend for J.P.?

    A. LDL less than 190 mg/dL and TG less than 300 mg/dL
    B. Any LDL and TG less than 500 mg/dL
    C. LDL less than 110 mg/dL and TG less than 500 mg/dL
    D. LDL less than 190 mg/dL and any TG

Questions 20 and 21 pertain to the following case.

E.L. is a 72-year-old man with kidney cancer who started treatment with pazopanib about 3 weeks ago. His medical history includes hyperlipidemia treated with atorvastatin and reflux/heartburn treated with OTC omeprazole. E.L.'s oncologist predicts that he has a life expectancy of about 2–3 years. E.L. returns to the clinic today for evaluation of adverse effects.

20. E.L.'s ECG today reveals a QTc interval of 510 milliseconds. Which one of the following best explains E.L.'s test result?

    A. Taking pazopanib with food
    B. Taking pazopanib on an empty stomach
    C. Taking pazopanib with omeprazole
    D. Taking pazopanib with atorvastatin

21. E.L.'s blood pressure today is 165/98 mm Hg, which is consistent with his home readings. Which one of the following is best to recommend for E.L.?

    A. Chlorthalidone
    B. Losartan
    C. Diltiazem
    D. Nifedipine

Learner Chapter Evaluation: Toxicities of Oral Targeted Chemotherapy.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Distinguish between the epidermal growth factor receptor (EGFR)/MAPK/ERK kinase (MEK) inhibitor rash and the hand-foot skin reaction, given symptomatology, and design appropriate prevention and management regimens.
13. Evaluate preventive strategies for agents associated with photosensitivity.
14. For the patient taking oral targeted treatment, assess the risk of QTc prolongation given concomitant medications and comorbidities, and devise a risk management plan.
15. Develop monitoring and treatment plans for vascular endothelial growth factor inhibitor–induced hypertension and left ventricular ejection fraction dysfunction.
16. Construct monitoring plans, treatment goals, and therapy plans for hypothyroidism, hyperlipidemia, and hyperglycemia associated with oral targeted cancer treatment.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Melanoma

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LEARNING OBJECTIVES

1. Demonstrate an understanding of the epidemiology of melanoma skin cancers and the role of screening for the prevention of skin cancer.
2. Evaluate the role of immunotherapy in the adjuvant treatment of melanoma.
3. Evaluate the role of ipilimumab, nivolumab, and pembrolizumab in the treatment of metastatic melanoma.
4. Justify the role of genetic analysis in treatment selection with BRAF/MEK tyrosine kinase inhibitors.
5. Distinguish the role of oral BRAF inhibitor therapy in the treatment of skin cancer.
6. Design a pharmacotherapy plan – including monitoring parameters, side effect management, and, where applicable, oncolytic virus therapy – for the patient with metastatic melanoma

ABBREVIATIONS IN THIS CHAPTER

CTLA-4	Cytotoxic t-lymphocyte antigen-4
HD	High dose
IRAEs	Immune-related adverse events
MAPK	Mitogen-activated protein kinase
OS	Overall survival
OR	Objective response
PD-1	Programmed cell death-1
PET	Positron emission tomography
PFS	Progression-free survival
RFS	Relapse-free survival
SLNB	Sentinel lymph node biopsy
UVA	Ultraviolet A
UVB	Ultraviolet B

Table of other common abbreviations.

INTRODUCTION

Epidemiology

The incidence of skin cancer is on the rise globally (Siegel 2016). The American Cancer Society (ACS) estimates that 5.4 million basal and squamous cell cancers, or non-melanoma skin cancers, will be diagnosed in 2016. In comparison, an estimated 76,380 people will be diagnosed with melanoma. Although non-melanoma skin cancer is the most common malignancy of the skin, cutaneous melanoma accounts for up to 75% of all skin-cancer related deaths (O'Bryant 2014). Melanoma is the fifth most common cancer in men and the seventh most common cancer in women; the average age at onset is 61 years (Siegel 2016). The incidence of melanoma is increasing rapidly in men but decreasing in young adults ages 15–19 (Siegel 2016). In 2016, an estimated 10,130 deaths will occur from melanoma of the skin (Siegel 2016). However, because of early detection and notable advances in treatment, the 5-year relative survival rates have increased to 92% (ACS 2016a). As with most malignancies, 5-year survival rates decline with more advanced disease. It is estimated that 82%–85% of patients with melanoma present with localized disease, 10%–13% with regional disease, and 2%–5% with distant metastatic disease (NCCN 2016).

Advances in surgery, chemotherapy, and immunotherapy for the treatment of melanoma have improved survival rates, but these also can be associated with significant side effects or toxicity. Pharmacists can have a significant impact on the management and treatment of melanoma. Skin cancer screening and prevention programs offer opportunities for pharmacists to assist in decreasing the incidence of melanoma.

Etiology

The cause of melanoma is not fully understood, but there are multiple environmental and patient-specific factors associated with the diagnosis. Exposure to sunlight, specifically ultraviolet B (UVB) radiation, has consistently shown a strong association, although prolonged exposure to ultraviolet A (UVA) radiation also has risk. Like most cancers, genetic factors have been linked to the incidence of melanoma. Familial atypical multiple mole syndrome has an overall lifetime cumulative risk of 100% because of a mutated CDKN2A, an encoder for two distinct proteins that ultimately inactivate p53 tumor suppressor gene (Eckerle 2009). Other genetic factors account for a fraction of the overall risk of melanoma; these include xeroderma pigmentosum, mutations in CDK4, BRCA2 mutations (3%–5% lifetime risk), melanocortin 1 receptor gene (MCIR), microphthalmia-associated transcription factor (MITF), and neural precursor cell expressed developmentally downregulated protein 9 upregulations. Activated BRAF (V600E) mutation in the mitogen-activated protein kinase (MAPK) signaling pathway is the most common somatic gene mutation and is found in about 50% of melanoma patients (Curtin 2005). Although less common, BRAF V600K mutation has also been identified.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of cancer and the development of melanoma
- General knowledge on sun protection factor (SPF)
- The mechanism of action of interferon

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Cancer Society (ACS). Cancer Facts & Figures 2016. 2016.
- Hauschild A, Gogas H, Tarhini A, et al. Practical guidelines for the management of interferon alpha – 2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer 2008;112:982-94.
- Kirkwood JM, Bender C, Agarwala S, et al. Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. J Clin Oncol 2002;20:3703-18.

Pathogenesis

Malignant transformation of skin melanocytes, dendritic pigmented cells, or transformation of preexisting nevocellular nevi leads to the development of melanoma. Melanocytes during fetal development migrate to various sites on the body (e.g., skin, uveal tract, meninges, ectodermal mucosa). The choroid of the eye and the epidermal-dermal junction of the skin house the majority of melanocytes; therefore, melanoma can arise from these areas or any area of the body with melanocytes.

The main function of melanocytes is to synthesize melanin to protect tissues from ultraviolet radiation-induced damage. The malignant transformation involves a series of morphologic stages from melanocytic atypia to atypical hyperplasia, radial growth phase, vertical growth phase, regional lymph node metastatic melanoma, and then to distant metastatic melanoma (Ribas 2015). Melanoma has the potential for metastasis with the onset of a vertical growth phase; therefore, thickness of a primary cutaneous melanoma lesion is an important prognostic factor in the staging and classification of the cancer (O'Bryant 2014).

Risk Factors

Patients who are white with fair hair (blonde or red), blue, green or gray eye color, and a high degree of freckling are at higher risk of developing melanoma if exposed to higher intensity sunlight. The age of exposure to the sun, the amount of exposure, and blistering sunburns are considered critical for the development of cutaneous melanoma. A meta-analysis confirmed that intermittent sun exposure with burning is more closely correlated with melanoma than chronic occupational exposure (Gandini 2005). Sun exposure is more hazardous during childhood and adolescence than during adulthood (Jen 2009). Exposure to sun lamps and tanning beds, especially as a young adult, is associated with increased risk of melanoma. A well-documented risk factor for melanoma is the presence of melanocytic nevi and atypical nevi (pigmented lesions or moles). There is a direct correlation between the amount of melanocytic nevi and the development of melanoma. In addition, 20% of melanoma cases develop from atypical nevi (Jen 2009).

PATHOPHYSIOLOGY

Histologic Subtypes

There are several histologic subtypes of melanoma that are descriptive only and are not used in the staging, treatment, or prognosis of melanoma. Superficial spreading melanoma, which makes up 70% of all melanoma cases, is the most common morphologic subtype. These lesions are typically more common in women than men, occur after the onset of puberty, and arise from a preexisting nevus. Lesions transition from a flat physical appearance to a more irregular and asymmetrical shape (Ribas 2015). Superficial spreading melanoma may occur at any body site but are more commonly found on the backs in men and the legs in women (O'Bryant 2014).

Lentigo maligna melanoma derives from lentigo maligna, in situ malignant cells without invasive growth. Lentigo maligna can be found on chronically sun exposed and damaged skin; in whites, it is typically located on the head and faces, and it occurs in about 10%–20% of melanoma cases. This histologic subtype has less propensity to metastasize and can be found in older patients. The most common subtype found in blacks, Asians, and Hispanics is acral lentiginous melanoma. These lesions can be found primarily on the palms of the hands, soles of the feet, and beneath the nailbeds (subungual melanoma). Acral lentiginous melanoma is not related to sun exposure. Mucosal melanoma is also a subtype of acral lentiginous melanoma that can be found on any mucosal surface.

Mucosal melanoma is most commonly found on the oropharyngeal mucosa, but it can also be found on the anal and rectal mucosa and the genital and urinary mucosa. Mucosal melanoma may go undiagnosed until clinically recognizable or until the lesion bleeds (O'Bryant 2014). Uveal melanoma, arising from the epithelium of the choroid, is an uncommon tumor but can rapidly progress to metastatic disease, most commonly in the liver. Uveal melanoma is the most common ocular malignancy in adults (Ribas 2015).

SCREENING AND PREVENTION

Guideline Recommendations

Improved survival rates result from resection of lesions at an earlier stage of development; this emphasizes the importance of early detection and prevention, especially for high-risk patients. Massive screening for all adults by a physician has never been demonstrated as cost-effective (Freedberg 1999). Therefore, the U.S. Preventive Services Task Force (USPSTF) finds insufficient evidence to assess the balance of benefits and harms of visual skin cancer screening in adults (USPSTF 2015). The American Academy of Dermatology (AAD) recommends skin self-examination as a mechanism of recognizing moles, marks, or changes in the skin that may be melanoma (AAD 2016).

The ABCDEs of melanoma can be used to describe or evaluate a questionable lesion based on the clinical features. Each lesion should be evaluated for *A*symmetry, irregular *B*orders, *C*olor (range in color or blue/black), *D*iameter (6 mm of greater is suspicious), and *E*volving in its characteristics (Abassi 2004). A mirror should be used to completely inspect the front and back of the body, forearms, upper arms, palms, back of the legs and feet, spaces between the toes, soles of the feet, back of the neck, scalp, neckline, and the buttocks area. Itching or bleeding of skin lesions are considered abnormal and patients should make an appointment with a board certified dermatologist. The AAD also recommends protection of skin from UV rays (preferably both UVA and UVB) by seeking shade, wearing protective clothing, and using a sunscreen with a sun protection factor (SPF) of 30 or higher. The use of tanning beds or sun lamps is discouraged. Annual clinical examinations are recommended for high-risk patients. Screening photography may be necessary to document size, shape, and location of moles (AAD 2016).

The ACS prevention program recommends avoiding direct exposure to the sun between 10 a.m. and 4 p.m.; wide-brimmed hats to shade face, ears, and neck; sunglasses; and clothing to block the arms, legs, and torso from UV rays. Like the AAD, ACS suggests education about avoiding tanning beds and sun lamps; use of sunscreen with at least an SPF of 30 on exposed skin; and appropriate use of screens and additional sun protection for patients at high risk of burning or who have prolonged sun exposure (ACS 2016b).

DIAGNOSIS AND PROGNOSIS

Clinical Presentation

Symptoms at the time of diagnosis vary with the location and extent of disease. Localized disease is found in 84% of patients at diagnosis; these patients are typically asymptomatic. Some patients may complain of a new or changing nevus associated with pruritus or site-specific bleeding. Many suspicious lesions, unrecognized by the patient, are found on physical examination by a primary care provider or dermatologist. Larger lesions are often noticeable, bulky, and more likely to be associated with symptoms.

Symptoms not associated with the suspicious lesion may suggest metastatic disease and warrant additional testing. Four percent of patients present with metastatic disease; symptoms associated with metastatic sites include shortness of breath, abdominal pain, bone pain, headaches, and mental status changes. In addition to a comprehensive physical examination, a family history may uncover additional risk factors for melanoma (Howlader 2014).

Diagnosis

Once identified, suspicious lesions should be excised or biopsied by a professional. Shave biopsies should never be performed to diagnose melanoma because they may interfere with the pathologic diagnosis. A full-thickness excisional biopsy is preferred with a margin of 1-3 cm (negative margins); this should be planned so as to not interfere with lymphatic mapping and sentinel lymph node biopsy (SLNB). Where an excision biopsy is not possible, an incisional biopsy with a full core thickness of skin and subcutaneous tissues should be conducted (NCCN 2016). In addition to a complete history, including prior removal of melanoma or other dysplastic nevi, a total body skin examination is recommended.

Staging

The American Joint Committee on Cancer staging system is the basis for categorization of melanoma based on clinical and pathologic information into four stages (Table 2-1 and Table 2-2). These stages can be further categorized into three

Table 2-1. Clinical Staging for Cutaneous Melanoma

Stage	Tumor	Node	Metastases	Description of Lesion
0	Tis	N0	M0	In situ non-invasive tumor
IA	T1a	N0	M0	≤ 1mm in thickness–no ulceration and mitosis < 1 mm^2
IB	T1b T2a	N0 N0	M0 M0	≤ 1mm in thickness–with ulceration or mitosis ≥ 1 mm^2 OR 1.01–2.0 mm–no ulceration
IIA	T2b T3a	N0 N0	M0 M0	1.01–2.0 mm–with ulceration OR 2.01–4.0 mm–no ulceration
IIB	T3b T4a	N0 N0	M0 M0	2.01–4.0 mm–with ulceration > 4.0 mm–no ulceration
IIC	T4b	N0	M0	> 4.0 mm–with ulceration
III	Any T	≥ N1	M0	Node positive and/or in-transit disease
IV	Any T	Any N	M1	Metastatic disease

Adapted with permission from: American Joint Committee on Cancer (AJCC), Chicago, Illinois.

Table 2-2. Pathologic Staging for Cutaneous Melanoma

Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b T2a	N0 N0	M0 M0
IIA	T2b T3a	N0 N0	M0 M0
IIB	T3b T4a	N0 N0	M0 M0
IIC	T4b	N0	M0
IIIA	T1-4a (no ulceration) T1-4a (no ulceration)	N1a (1 micrometastatic node) N2a (2 – 3 micrometastatic node)	M0
IIIB	T1a – 4b (with ulceration) T1 – 4b (with ulceration) T1 – 4a (no ulceration) T1 – 4a (no ulceration) T1 – 4a/b (+/- ulceration)	N1a (1 micrometastatic node) N2a (2-2 micrometastatic nodes) N1b (1 macrometastatic node) N2b (2-3 macrometastatic node) N2c (in-transit metasatellites with satellites no metastatic nodes)	M0 M0 M0 M0 M0
IIIC	T1 – 4b (with ulceration) T1-4b (with ulceration) Any T	N1b (1 macrometastatic node) N2b (2-3 macrometastatic node) N3 (4+ metastatic nodes)	M0 M0 M0
IV	Any T	Any N	M1

Adapted with permission from: American Joint Committee on Cancer (AJCC), Chicago, Illinois.

broader groups including localized disease with no evidence of metastases (stage I-II), regional disease (stage III), and distant metastatic disease (stage IV). Ulceration, mitotic rate, and Breslow tumor thickness are three of the most important characteristics in staging localized disease.

Ulceration is a pathologic description; this occurs when the epidermal layer overlying the tumor is not intact. Ulceration is indicative of aggressive disease and worse prognosis. Breslow thickness quantifies tumor thickness to the nearest tenth of a millimeter, from the top of the granular layer of the overlying epidermis to the deepest contiguous invasive melanoma cell (NCCN 2016). Breslow thickness replaces the historical Clark's level assessment, which was an evaluation of the level of invasion based on landmarks (epidermis, papillary dermis, reticular dermis). Clark's level may still be used in nonulcerated lesions where the mitotic rate is not determined in lesions 1 mm^2 or less. Mitotic rate is an indicator of tumor proliferation and is measured as the number of mitoses per mm^2 (Jemal 2011). Mitotic rate of 1 mm^2 or greater correlates with worse prognosis. Metastatic nodes and clinical node status (nonpalpable vs. palpable) are the most important predictors of survival in patients with regional disease.

Patients can be clinically staged after histopathologic microstaging of the primary tumor; a complete history and physical, which includes examination of locoregional area and draining lymph nodes; and a complete skin examination (NCCN 2016). Patients with clinical localized stage I-II disease or lesions that are more than 1 mm thick may be further staged with lymphatic mapping with SLNB. In patients with intermediate-thickness melanoma, a SLNB can be performed to determine if additional lymph node mapping or an axillary lymph node dissection is necessary. Sentinel lymph node biopsy is a minimally invasive procedure that determines if the sentinel lymph node, the first node in the basin to which the primary lesion drains, is positive for disease. The SLNB is associated with low false-negative rates and low complication rates (Morton 2006).

If the sentinel lymph node is negative, regional lymph node dissection is not recommended. Additional work-up for these patients includes establishing a set of baseline images for future comparison as the patient progresses through treatment. Positron emission tomography (PET) or CT are useful in patients except for those with clinically localized melanoma because these images have very low yield and poor sensitivity (NCCN 2016). In stage IV disease, an MRI or CT with contrast should be performed to rule out brain metastases.

Routine blood tests are not recommended in patients with stage I or II disease, but lactate dehydrogenase (LDH) is recommended in patients with metastatic disease as a prognostic factor. Establishing the BRAF mutation status is also recommended in all patients with suspected metastatic disease. The oncologist's discretion may be used for additional blood testing.

Prognosis

Stage of the disease at the time of diagnosis is the best indicator of prognosis. Additional contributors to the overall outcome include tumor thickness, level of tumor invasion, and ulceration. Tumor growth patterns, histologic subtype, LDH level, mitotic rate, sex, and age also influence survival. Location of the melanoma lesion has a relationship to survival: melanomas on the axial, neck, head, and trunk are associated with a lower survival than tumors found on the extremities (NCCN 2016). Additional prognostic factors that may negatively affect advanced disease include Eastern Cooperative Oncology Group (ECOG) performance status of 1 or greater; male sex; prior immunotherapy; and involvement of the GI tract, liver, pleura, or lung (NCCN 2016).

Patients with local disease and tumors of 1 mm or less have a 5-year survival rate grater than 90%. Survival rates decrease as melanoma stage increases. The 5-year survival rate for patients with stage IV disease is 10%. Patients with larger melanoma lesions, including those with thickness greater than 4 mm and lymph node involvement, have a higher risk of relapse (NCCN 2016). Elderly patients (especially those older than 70) have a worse prognosis. Although melanoma in African Americans is rare, it is typically associated with a worse prognosis. Brain, lymph nodes, and lungs are the most common sites of metastases.

TREATMENT

Surgery

Staging affects treatment options and management recommendations for patients with cutaneous melanoma. Surgery with excisional removal is the primary treatment for patients with localized disease and is often curative (O'Bryant 2014). An important aspect of surgical removal is maintaining negative margins. Local recurrence and overall survival (OS) are dependent on excisional margins. For primary tumors less than 1 mm thick, the margin width must be at least 1 cm wide. Larger tumors (1.01–2 mm thick) require a margin of 1–2 cm. Tumors that are greater than 2 mm thick require 2-cm margins. After surgery, routine screening and follow-up is recommended for all patients. The specific follow-up time is controversial; however, the patient is at greatest risk of relapse and recurrence in the first 2 years (NCCN 2016).

Beyond a cure, the role of surgery is less clear, but it may offer palliation for patients with isolated metastases (Wargo 2009). Isolated metastatic lesions may be resected if the lesions are assessable and it may add quality of life and lessen symptoms. Surgery also may extend survival and long-term disease control in select patients with metastatic melanoma (Tsao 2004).

Adjuvant Treatment

The risk of relapse and death after resection of a local or regional cutaneous melanoma is the primary determinant for use of adjuvant therapy. For patients with stage IB or II,

or node negative early stage disease, adjuvant treatment options include clinical trial or observation. No data have shown prolonged survival with additional treatment after the initial curative surgery. Clinical trials, where available, are an opportunity to participate in a discovery of a new therapy or type of treatment to reduce disease recurrence. If a clinical trial is not available or not desired, observation is suggested with scheduled follow-up and screening, although frequency and duration have not been determined. Clinical trial, observation, or adjuvant interferon are currently recommended for patients with stage IIB, stage IIC, or stage III disease.

Interferon alfa – 2b is one of the oldest and most controversial therapies for the adjuvant treatment of melanoma. Because of melanoma's ability to respond and interact with the immune system of its host, interferon's immunomodulatory and antiangiogenic properties has long been proposed to affect the growth of melanoma. Low-dose, intermediate-dose, high-dose (HD), and pegylated interferon have been evaluated. The use of low dose or intermediate dose interferon is discouraged in high-risk patients with melanoma because no study has shown OS improvement (NCCN 2016).

Multiple studies have evaluated the use of HD interferon. The ECOG 1684 study included patients with stage IIB and III melanoma. Patients were randomized to either interferon alfa – 2b 20 million units/m^2/day intravenously for 5 days a week for 4 weeks, then 10 million units/m^2 subcutaneously three times a week for 48 weeks versus observation. A median follow-up of 6.9 years revealed significantly longer relapse-free survival and OS rates with HD interferon. The FDA approved interferon alfa – 2b based on these results. After 12.6 years follow-up, there was a statistically significant difference in relapse-free survival (37% vs. 26%) in the interferon arm versus observation. There was no difference in 5-year OS (46% vs. 37%) (Kirkwood 1996). Subsequent studies by the same authors resulted in similar outcomes, with no statistical significance in OS (Kirkwood 2000, 2001).

The European Organization for Research and Treatment of Cancer (EORTC) 18991 study evaluated the use of pegylated interferon for 5 years in completely resected patients with stage III melanoma versus observation alone. Patients received 6 mcg/kg subcutaneously per week for 8 weeks, followed by 3 mcg/kg per week for 5 years. Four-year relapse-free survival rates were 45.6% versus 38.9% (p=0.01), but no statistical difference was seen in OS (56.8% vs. 55.7%, p=0.78). The discontinuation rate was higher (31%) in the interferon group because of a higher rate of grade 3 and 4 toxicity. Quality of life was also decreased (Eggermont 2008).

According to multiple meta-analyses, the evidence is conflicting and controversial when evaluating OS benefit with adjuvant interferon therapy, but significant relapse-free survival benefit has been confirmed (NCCN 2016). Of the seven studies included in the most recent meta-analysis, OS was not significantly different between adjuvant HD interferon and observation alone (HR 0.93; 95% CI, 0.78–1.12; p=0.45) (Petrella 2012). There is consensus from NCCN that HD interferon improves disease-free survival, but there is a disagreement on its impact on OS (Petrella 2012). Treatment with HD interferon is still included in national guideline treatment algorithms as an option in the adjuvant setting. Because of its high toxicity profile, HD interferon may have a role in certain settings; if used, the recommendation is for at least a year of HD interferon or pegylated interferon with planned maximal duration of 5 years (2B recommendation) (NCCN 2016). Clinicians should review the potential risks versus benefits and have a discussion about the side effect profile before patients make a decision about adjuvant treatment with interferon.

A novel immunologic approach to fighting malignancies is the blockade of the cytotoxic T-lymphocyte antigen-4 (CTLA-4) receptor with monoclonal antibodies. The CTLA-4 receptor, a molecule on T cells, is believed to play a critical role in regulating natural immune responses. The absence or presence of CTLA-4 can augment or suppress the immune system's T-cell response in fighting disease. CTLA-4 inhibits T-cell responses, thereby applying brakes to an ongoing immune response. Transient blockade of the triggering of CTLA-4 can lead to enhancement of T cell responses. Ipilimumab, an IgG isotype antibody, is the first anti-CTLA-4 agent with label approved for use in melanoma. Approved initially in the metastatic setting, ipilimumab demonstrated the ability to induce tumor regression, prolong time to progression, and increase OS in both previously treated and untreated metastatic melanoma. In October of 2015, ipilimumab also received FDA label approval for adjuvant treatment.

A double-blind, phase III trial was conducted in patients with previously untreated, lymph node resected, stage III cutaneous melanoma. Patients received either ipilimumab 10 mg/kg or placebo every 3 weeks for four doses, then every 3 months for up to 3 years. At a median follow-up of 2.74 years, the median recurrence-free survival was 26.1 months (95% CI. 19.3–39.3) in the ipilimumab group versus 17.1 months in the placebo group (HR 0.75; 95% CI, 0.64–0.90; p=0.0013). Three-year recurrence-free survival was 46.5% (95% CI, 41.5–51.3) versus 34.8% (95% CI, 30.1–39.5). There was a 52% discontinuation rate because of adverse events in the ipilimumab arm during the initial four-dose period; this was likely caused by the higher dosing of 10 mg/kg (including five drug-related deaths). Grade 3–4 immune-related adverse events in the ipilimumab group included GI (16%), hepatic (11%), and endocrine (8%) effects (Eggermont 2015). A recent update at 5.3 years demonstrated an overall survival benefit of 65.4% in the ipilimumab group versus 54.4% in the placebo group (HR for death, 0.72; 95% CI, 0.58–0.88; p=0.001) (Eggermont 2016). The NCCN now recognizes ipilimumab as an option for adjuvant treatment (category 1 recommendation) with the caveat that careful selection of patients is warranted because of the toxicity profile.

METASTATIC DISEASE TREATMENT

Ipilimumab

The systemic therapy options for the treatment of metastatic melanoma have increased and the treatment landscape is rapidly changing. With the development of novel compounds with unique mechanisms of action and side effect profiles, traditional chemotherapeutic agents and older immunotherapy options are no longer primary first-line treatments.

Ipilimumab received FDA label approval in 2011 after a phase III study proved OS benefit in patients with metastatic melanoma. Patients with unresectable stage III or stage IV melanoma that failed to improve with other therapies were randomized in a 3:1:1 ratio to receive ipilimumab 3 mg/kg plus a glycoprotein 100 (gp100) vaccine every 3 weeks for four cycles; ipilimumab plus a gp100 placebo; or placebo plus gp100 vaccine. The primary end point was OS. Secondary end points included best overall response rate, duration of response, and progression-free survival (PFS). Median OS was 10 months in the ipilimumab combination arm (95% CI, 8.5–11.5) versus 10.1 months in the ipilimumab alone arm (95% CI, 8–13.8) versus 6.4 months in the gp100 arm (95% CI, 5.5–8.7; HR 0.68; p<0.001). Patients with stable disease for 3 months duration after week 12 or a confirmed partial/complete response were offered additional courses of therapy if disease progressed. Of the 403 patients randomly assigned in this study, 31 patients underwent reinduction (8 patients with ipilimumab, 23 with ipilimumab combination); 15 of 23 patients achieved a partial response or stable disease after reinduction in the combination arm; 5 of 8 patients in the ipilimumab alone group had a partial response or stable disease (Hodi 2010). This was the first trial to show improved OS in the metastatic melanoma setting.

Because of the stimulation and infiltration of T cells in the skin and GI tract, ipilimumab causes significant immune-related adverse events (IRAEs). In the landmark trial, 60% percent of patients reported IRAEs, with 10% of these resulting in grade 3 or grade 4 events (Hodi 2010). Some effects may be mild and self-limiting. The most commonly documented IRAEs include rash, colitis, hepatitis, and hypophysitis.

Ipilimumab was also evaluated in a phase III study in first-line, untreated metastatic melanoma to determine the value of combining ipilimumab with traditional chemotherapy. Patients were randomized to dacarbazine plus ipilimumab or dacarbazine plus placebo. Overall survival was 11.2 months in the combination arm and 9.1 months in the control arm; 3-year survival rates were 20.8% and 12.2%, respectively. Grade 3 and 4 adverse events were higher in the ipilimumab combination arm (56%) (Robert 2011). A major criticism of this study was that the dose in the combination arm (10 mg/kg) was more than three times higher than the FDA-approved dose. Therefore, data from this study are difficult to extrapolate. The NCCN guidelines recommend using the approved dose of ipilimumab, and higher doses should be reserved for clinical trials (NCCN 2016).

Programmed Death-1 Inhibitors

Melanomas can also express programmed death-1 ligand, which can bind to the programmed death-1 (PD-1) site on antigen stimulated T-cells. The binding results in inhibition of T-cell function and the body's immune response. The PD-1 inhibitors can block or inhibit the binding of the ligand to the PD-1 site, therefore reactivating the body's immune response. In 2015, pembrolizumab, a humanized monoclonal antibody, was the first PD-1 inhibitor to receive FDA label approval for use after disease progression on ipilimumab. In the KEYNOTE-001 expansion study, patients with ipilimumab-refractory metastatic melanoma were randomized to receive pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks until progression of disease or toxicity. After a median follow-up of 8 months, the OR rate was 26% at both doses. The adverse effect profiles were very similar including fatigue (33% vs. 37%), pruritus (26% vs. 19%), and rash (18% vs.18%) in the 2 mg/kg and 10 mg/kg arms (Robert 2014).

The KEYNOTE-006 study, a phase III control study, compared pembrolizumab to ipilimumab in patients with unresectable stage III or stage IV melanoma whose disease had previously failed one line of treatment. Patients received either pembrolizumab 10 mg/kg intravenously every 2 weeks, pembrolizumab 10 mg/kg every 3 weeks, or ipilimumab 3 mg/kg every 3 weeks for four cycles. Six-month PFS was 47.3% (pembrolizumab every 2 weeks) versus 46.4% (pembrolizumab every 3 weeks) versus 26.5 % (ipilimumab every 3 weeks), respectively (p<0.001). Twelve-month OS was 74% in the pembrolizumab every 2 weeks arm versus 58% in the ipilimumab arm. Response rates were very similar between the two pembrolizumab arms (33.7% vs. 32.9%), but were three times as high as compared with the ipilimumab arm (11.9%). Duration of response was not reached at 7.9 months. Grades 3–5 adverse events were higher in the ipilimumab arm versus the pembrolizumab arms (19.9% vs. 13.3% vs. 10.1%) (Robert 2015). This study proved that pembrolizumab not only had higher PFS and OS but less toxicity than ipilimumab and could be a first-line option for treatment in these patients.

Nivolumab, a fully human monoclonal antibody, was the second PD-1 inhibitor to get FDA label approval in 2014. Nivolumab was originally approved for patients who had failed a trial of ipilimumab and had tumors that expressed the BRAF V600 gene mutation. A phase I dose-escalation, cohort expansion study evaluated patients with multiple tumor types (melanoma, non-small cell lung cancer, kidney, colorectal, and castrate resistant prostate cancer) who had received at least one prior line of therapy. Patients received escalating doses of nivolumab every 3 weeks until progression or toxicity. After dose escalation was completed, each dose cohort was expanded to accrue about 16 patients with melanoma (Topalian 2014).The median OS was 16.8 months,

with 62% of the patients remaining alive at year 1 and 43% remaining alive at year 2. The most common toxicities were fatigue (32%), rash (23%), and diarrhea (18%) (Topalian 2014).

In a phase III study (CHECKMATE 066) in treatment naïve patients with metastatic melanoma, 418 patients without a BRAF mutation received either nivolumab 3 mg/kg every 2 weeks and dacarbazine-matched placebo every 3 weeks or dacarbazine 1000 mg/m^2 every 3 weeks and nivolumab-matched placebo every 2 weeks. The primary end point of OS was 72.9% (95% CI, 65.5–78.9) for the nivolumab arm versus 42.1% (95% CI, 33–50.9) in the dacarbazine group (HR 0.42, p<0.001). Median PFS was 5.1 months versus 2.2 months in the dacarbazine group (HR 0.43, p<0.001). Fatigue (19.9%), pruritus (17%), and nausea (16.5%) were the most common adverse events (Robert 2015). Nivolumab is now approved for use as first-line therapy in patients with unresectable and metastatic melanoma. Recent pharmacokinetic data suggest the predicted exposure of a flat dose of 240 mg overlaps with the range observed at the 3 mg/kg dose in an 80-kg patient (Data on File: NIVO 166 and NIVO 170). The approved standard dose of nivolumab is now 240 mg when given as a single agent for melanoma.

BRAF and MEK Inhibitors

Mutated BRAF allows for MAPK independent signaling, which can increase tumor cell proliferation and survival. The BRAF inhibitors bind to the tyrosine kinase of the mutant BRAF V600; this inhibits MAPK signaling and leads to tumor apoptosis. Vemurafenib, a BRAF inhibitor, was approved in 2011 in patients with metastatic melanoma or unresectable melanoma whose tumors express the BRAF V600 gene mutation.

In the BRIM-3 trial, a phase III study comparing vemurafenib versus dacarbazine in previously untreated patients, more than 600 patients were randomized to either 960 mg twice daily of oral vemurafenib or 1000 mg/m^2 of dacarbazine intravenously every 3 weeks. Primary end points were OS and PFS. After 6 months of treatment, OS was 84% versus 64% (HR 0.37; 95% CI, 0.26–0.55; p<0.001) with objective response rates of 48% and 5%, respectively. Progression-free survival was 5.3 months versus 1.6 months, with a median time to response at 1.45 months (Chapman 2011). The most common toxicities with vemurafenib include rash, photosensitivity, fatigue, alopecia, arthralgia, and keratoacanthoma or squamous cell carcinoma. As a second-line treatment, vemurafenib showed promising results with PFS of 6.8 months in disease failing HD aldesleukin (also known as interleukin-2) and ipilimumab with a median OS of 15.9 months (Sosman 2012).

Dabrafenib is the second BRAF inhibitor approved for first-line use. In a phase III open label study, patients with metastatic or unresectable melanoma with the V600E mutation were randomized to either receive either 150 mg of dabrafenib twice daily by mouth or dacarbazine 1000 mg/m^2 intravenously every 3 weeks; PFS was 5.1 months versus 2.7 months in the dacarbazine group (HR 0.3; 95% CI, 0.18–0.51). Fever, fatigue, arthralgia, headache, and skin-related toxic effects were the most common adverse events (Hauschild 2012). Dabrafenib's side effect profile is similar to vemurafenib, but there is a higher incidence of epithelial skin lesions with dabrafenib (although this has not been studied in head-to-head trials).

Another strategy to shut down the mutation driven MAPK signaling is to inhibit MEK, the kinase immediately downstream of BRAF (Jarkowski 2014). Trametinib, a MEK1 and MEK2 inhibitor, received FDA label approval in 2013 for use as monotherapy in BRAF mutated advanced melanoma. The METRIC study was a phase III two-arm study that randomized patients to trametinib 2 mg by mouth daily or traditional chemotherapy with dacarbazine 1000 mg/m^2 IV every 3 weeks or paclitaxel 175 mg/m^2 IV every 3 weeks. Patients had either stage IIIC or stage IV melanoma and had been failed by at least one prior therapy. Trametinib versus dacarbazine produced an overall response rate of 22% and 8%. Median PFS was 4.8 months versus 1.5 months (HR 0.45, 95% CI, 0.33–0.63, p<0.001) favoring trametinib. Despite crossover from the chemotherapy arm, 6-month survival rate was 81% versus 67% in the chemotherapy group (HR 0.54; 95% CI, 0.32–0.92; p=0.01) (Flaherty 2012). Updated survival data was later presented and the median OS was 15.6 months in the trametinib arm, and 11.5 months in the chemotherapy arm (HR 0.78; 95% CI, 0.57–1.06; p=0.0912) but failed to reach statistical significance (Schadendorf 2013). Hyperproliferative skin lesions seen with BRAF inhibitors were not observed with trametinib. Rash, diarrhea, peripheral edema, and fatigue were the most common toxicities observed with trametinib (Jarkowski 2014).

BRAF and MEK Inhibitor Combination Therapy

Because preclinical evidence revealed improved responses and lower rates of cutaneous squamous cell carcinomas, dual MAPK blockade with dabrafenib and trametinib was investigated in a phase I/II study. In a multiple cohort four-part study, participants were randomized to receive single agent dabrafenib 150 mg twice daily by mouth, dabrafenib 150 mg twice daily with trametinib 1 mg daily, or dabrafenib 150 mg twice daily with trametinib 2 mg daily. Crossover from single agent therapy to a combination arm was allowed if patients experienced progression. Patients had advanced melanoma with positive BRAF mutation status and could have failed one prior therapy excluding other BRAF or MEK inhibitors. Unique to this study, patients with treated brain metastases and at least a 3-month history of stable disease were not excluded and were allowed to enroll. Median PFS was 9.4 months in the 150/2 arm versus 5.8 months in the monotherapy group (HR 0.39; 95% CI, 0.25–0.62; p<0.001). The overall response rates were 76% in the 150/2 arm versus 54% in the dabrafenib monotherapy arm (p=0.03). The incidence of squamous cell carcinoma was lower in the combination versus the dabrafenib

Patient Care Scenario

Two months ago, a 45-year-old non-Hispanic white man with metastatic melanoma was initiated on vemurafenib 960 mg twice daily. Baseline transaminases and chemistries were normal. An ECG revealed QTc of 440 ms with normal rate and rhythm. The patient had no other significant medical history.

Day	15	30
Potassium (mEq/L)	4	5.2
Magnesium (mg/dL)	1.8	2.5
Calcium (mg/dL)	9.5	8.1

Electrolytes were monitored closely and an ECG was ordered on day 30 that revealed a QTc > 545 ms. The patient is scheduled for follow-up today. What is best to recommend to the treating oncologist before this patient's next dose of therapy?

ANSWER

According to the package insert for vemurafenib, therapy should be withheld in patients who develop QTc > 500 ms (grade 3 toxicity). Upon recovery to QTc ≤ 500 ms (grade ≤ 2), restart at a reduced dose. Vemurafenib treatment should be permanently discontinued if the QTc interval remains > 500 ms and increased > 60 ms from pretreatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias). The patient may be treated in the outpatient setting for the electrolyte abnormalities to reduce the incidence of additional cardiac abnormalities.

1. Chapman PB, Hauschild A, Robert C et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507-16.
2. Vemurafenib manufacturer's package inserts.
3. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology— Melanoma, version 3. 2016.

arm (7% vs. 19%, p=0.09), but was not statistically significant. The combination arms were associated with more pyrexia, GI side effects, cardiovascular issues, neutropenia, and ocular toxicity (Flaherty 2012). Updated data confirms a median PFS of 3.6 months (95% CI, 2–4) and median OS was 11.8 months (95% CI, 8–25) (Johnson 2014). In a randomized, open label, study (COMBI-v) evaluating dabrafenib and trametinib combination versus vemurafenib single agent therapy in patients with a BRAF V600 mutation, PFS was 11.4 months in the combination arm versus 7.3 months in the single agent arm (HR 0.56; 95% CI, 0.46–0.69; p<0.001). As paralleled in other studies, rates of alopecia and squamous cell carcinoma were lower in the combination arm (Robert 2015).

Cobimetinib, a potent, selective MEK inhibitor, received FDA label approval in 2015. In phase I studies, diarrhea, rash, fatigue, and edema were the most common side effects when used as a single agent (Ribas 2014). In addition to improving response rates and decreasing side effects, BRAF and MEK combination therapy has shown a decrease in resistance mechanisms. In a phase III study (Co-BRIM), patients with previously untreated unresectable or locally advanced or metastatic BRAF V600 mutation-positive melanoma were randomized to receive either vemurafenib or cobimetinib combination therapy or vemurafenib and placebo. Patients with previously treated brain metastases were eligible for enrollment if they had stable disease for at least 3 weeks. The primary end point was PFS. Secondary end points included overall survival, duration of response, and safety. Vemurafenib was administered at 960 mg twice daily (in both control and combination arms) with cobimetinib 60 mg daily for 21 days, followed by 7 days off. In the combination arm, the median PFS was 9.9 months versus 6.2 months in the control arm (hazard ratio 0.51; 95% CI, 0.39-0.68; p < 0.01). Nine-month OS rates at the interim analysis were 81% in the combination arm and 73% in the control arm. In the combination arm, the duration of response was not met but was 7.3 months in the control arm. The number of squamous cell lesions was decreased in the combination arm, but the combination therapy resulted in a higher incidence of grade 3 adverse events (65% vs. 59%) (Larkin 2014).

PD-1 Inhibitor and Ipilimumab Combination Therapy

Recent data pertaining to combination immunotherapy in patients with and without BRAF mutation status has complicated the decision process when determining the best first-line therapy for metastatic melanoma. One study randomized patients with unresectable previously untreated Stage III or IV melanoma (regardless of BRAF mutation status) in a 2:1 ratio to either nivolumab 1 mg/kg and ipilimumab 3 mg/kg every

Pivotal Study That May Change Practice

Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.

Setting: Ipiliumab, an anti-CTLA-4 antibody, was the first agent to show improved overall survival in a large randomized trial in metastatic melanoma patients. Nivolumab, a PD-1inhibitor, was initially approved for use in patients who progressed while being treated with ipilimumab. The results of a phase II study showed promising results with the use of combination therapy (ipilimumab and nivolumab). The CHECKMATE 067 study was conducted to evaluate the safety and efficacy of nivolumab alone or in conjunction with ipilimumab in comparison with ipilimumab alone in patients with untreated melanoma.

Design: Randomized, double-blind, phase III trial where untreated metastatic melanoma patients were randomized 1:1:1 to nivolumab 3 mg/kg every 2 weeks with placebo, nivolumab 1 mg/kg every 3 weeks and ipilimumab 3 mg/kg every 3 weeks for four doses, or ipilimumab 3 mg/kg every 3 weeks for four doses with placebo. The primary end points were PFS and OS. Secondary end points included objective response rate, PD-L1 expression, and safety. Planned sample size was 915 patients. For PFS, the number of events estimated to be observed at a follow-up of at least 9 months would give the study about 83% power to detect an average hazard ratio of 0.71 at a type I error rate of 0.005 (two-sided) for all comparisons.

Outcomes: A total of 1296 chemotherapy naïve patients at 137 centers globally were enrolled and 945 patients were randomized to receive one of the three treatments. The median PFS was 11.5 months (95% CI, 8.9–16.7) with combination nivolumab and ipilimumab compared with 2.9 months (95% CI, 2.8–3.4) with ipilimumab alone (HR 0.42; 99.5% CI, 0.31–0.57; p<0.001), and 6.9 months (95% CI, 4.3–9.5) with nivolumab (HR 0.57; 99.5% CI, 0.43–0.76; p<0.001); the OS data has not matured. Investigator assessed objective response rates were 43.7% (95% CI, 38.1–49.3) in the nivolumab group, 57.6% (95% CI, 52–63.2) in the nivolumab and ipilimumab group, and 19% (95% CI, 14.9–23.8) in the ipilimumab group. In patients with PD-1 ligand positive tumors, median PFS was 14 months in the nivolumab and ipilimumab and nivolumab alone group. The PFS was 11.2 months (95% CI, 8.0 to not reached) vs. 5.3 months (95% CI, 2.8–7.1) in the PD-1 negative tumors. Grade 3 or 4 adverse events related to study treatment occurred in 16.3% of the patients in the nivolumab group, 55% of those in the nivolumab plus ipilimumab group, and 27.3% of those in the ipilimumab group.

Impact: These findings support the use of nivolumab with ipilimumab as first-line treatment in untreated patients with metastatic melanoma regardless of PD-1 status. Overall survival data for this combination is not yet mature but appears to be promising. Health care professionals should review potential benefits and risks of combination therapy with metastatic melanoma patients before initiating treatment.

3 weeks for four doses or ipilimumab 3 mg/kg every 3 weeks for four doses. Both arms went on to either receive maintenance therapy with either nivolumab or placebo. In patients with BRAF wild-type tumors, objective response rates were 61% in the combination group and 11% in the ipilimumab monotherapy arm (p<0.001). Similar results were observed in the patients with BRAF mutant tumors. Median PFS was not met in the combination arm and was 4 months in the ipilimumab arm. Drug-related adverse events of grade 3 and 4 were higher in the combination arm and occurred in 54% of patients versus 24% in the ipilimumab alone group (Postow 2015). The combination therapy appears to be superior to single agent therapy, but with a higher rate of adverse events. The results from this trial resulted in approval of the indication of combination therapy with ipilimumab.

Nivolumab was also studied in combination with ipilimumab without maintenance therapy in previously treated unresectable patients with stage III or IV melanoma with similar results. The CHECKMATE 067 study evaluated effects of PD-1 tumor positivity on outcomes. In patients with tumors positive for the programmed death-ligand 1 (PD-L1), the median PFS was 14 months in the nivolumab plus ipilimumab group and in the nivolumab group, but in patients with PD-L1–negative tumors, PFS was longer with the combination therapy than with nivolumab alone (11.2 months [95% CI, 8.0 to not reached] vs. 5.3 months [95% CI, 2.8–7.1]) (Larkin 2015).

Chemotherapy

Dacarbazine, temozolomide, and paclitaxel with or without carboplatin are common chemotherapy regimens that were used in the treatment of metastatic melanoma before the approval of the newer, novel compounds. These therapies demonstrated modest response rates of less than 20% when used in first-line or second-line treatments. Additionally, the side effect profile is similar to other traditional chemotherapy agents (e.g., myelosuppression, alopecia, nausea/vomiting, rashes). One major benefit of temozolomide is its ability to cross the blood-brain barrier, enabling activity in patients with brain metastases (Middleton 2000). Patient-specific factors should be considered if a traditional therapy is used because these agents have significant effects on quality of life with little response benefit.

Interleukin-2

Interluekin-2 (IL-2), the original immunotherapy used for the treatment of melanoma, has reported response rates as high

as 15%–25% but also significant toxicity (Atkins 1999). Administration requires hospitalization to monitor for signs and symptoms of cytokine-induced capillary leak syndrome, pruritus, constitutional symptoms, changes in renal and liver function, and nausea/vomiting. One major disadvantage in using IL-2 is determining the appropriate dose because the FDA-approved doses and those used in clinical trials are associated with extremely high rates of toxicity. These toxic effects may limit the ability to use these therapies in patients with major comorbidities or poor performance status scores. Unfortunately, treatment-related mortality is high (Atkins 1999). The use of IL-2 is not recommended first line for the treatment of metastatic melanoma but may be considered if no contraindications exist after several lines of treatment have failed.

Biochemotherapy

Biochemotherapy is the combination of traditional chemotherapy and biological therapy. In a small phase III randomized trial, biochemotherapy (dacarbazine, cisplatin, vinblastine with IL-2, and interferon alfa) was compared with chemotherapy alone (dacarbazine plus cisplatin plus vinblastine). Response rates in the biochemotherapy arm were 48% versus 25% in the chemotherapy alone arm. Median survival was 11.9 months versus 9.2 months, respectively (Eton 2002). However, a meta-analysis evaluating over 18 biochemotherapy trials for the treatment of metastatic melanoma found that in more than 2600 patients, response rates were increased but OS was not improved (Ives 2007).

Intralesional Therapy

Studies have been ongoing for several years evaluating the benefit of local treatment of unresectable cutaneous melanoma lesions. Talimogene laherparepvec is a genetically modified herpes virus that integrates and produces granulocyte macrophage colony-stimulating factor GM-CSF. After lysis of the tumors, antigens with GM-CSF promote antitumor immune response. Each lesion is injected up to a maximum of 4 mL of 10^6 (1 million) plaque-forming units (PFU) per mL per site for the initial dose. Subsequent doses are 4 mL of 108 (100 million) PFU per mL. Talimogene laherparepvec must be kept at -90°C to -70°C.

In a randomized phase III study, patients were randomized to either talimogene laherparepvec or granulocyte macrophage colony-stimulating factor intralesionally. Durable response rates were 16.3% versus 2.1% in the colony-stimulating factor arm. No significant OS was seen, and this therapy had no effect on visceral metastases. Patients in this study had complete and partial responses for at least 6 months (Andtbacka 2015). This agent is sensitive to acyclovir and therefore it may interfere with virus therapy if taken concomitantly. Health care workers who are pregnant or immunocompromised should not prepare or administer the drug. Injection site reactions and complications are common including cellulitis, ulcerations, and non-healing wounds. Flu-like symptoms, nausea, vomiting, and diarrhea are also common with this therapy. Prophylaxis with OTC medications or even prescription therapies may be appropriate in these patients to prevent the side effects.

TREATMENT DECISIONS

Treatment decisions for initial treatment and subsequent therapy for metastatic melanoma can be complicated. The NCCN guidelines recommend treatment with PD-1 inhibitor either with nivolumab or pembrolizumab, as a single agent or nivolumab/ipilimumab combination therapy. Patients with BRAF-mutant melanoma who have symptomatic disease or who have progressed despite immunotherapy should be considered for targeted therapies. The NCCN guidelines recommend targeted therapies as first-line therapy if clinically necessary for a quick response (category 1 recommendation). Combination therapy is preferred (category 1 recommendation) but single agent BRAF inhibitor can be considered.

The onset of action for both combination therapy and single-agent therapy with a BRAF inhibitor is very quick, averaging less than 2 months. Half of patients treated with monotherapy relapse around 6 months because of drug resistance. Careful consideration of patient comorbidities, medication profile, treatment side effect profile, performance status, and cost should take priority in order to make the best treatment decision. If patients experience disease progression and have a good performance status, additional treatment options are available including immunotherapy, targeted therapy, high-dose IL-2, biochemotherapy, chemotherapy, and clinical trials. The selection of the specific agent would be dependent on what agent the patient received for first-line treatment. Clinical trials are under way to address unanswered questions regarding the optimal sequencing and/or combination of these agents

The cost of novel cancer immunotherapy agents and targeted therapy is quite high. Insurance coverage may vary and include prior authorization requirements such as BRAF testing. Therefore, pharmacists may be involved in enrolling patients into assistance programs, seeking preauthorization, or assessing copayments. Cost utilization and cost-effectiveness analysis are limited with the new therapies in this setting. In the adjuvant setting, interferon-alfa has been found to be cost-effective, although its clinical benefits are controversial (Johnson 2015). A pharmacoeconomic analysis evaluating ipilimumab in the second-line setting as compared with best supportive care resulted in a gain of 1.88 quality life years with an incremental cost of $146,716 (Barzey 2013).

MONITORING

Follow-up

Despite newer treatment options, follow-up and surveillance recommendations are lacking. The follow-up schedule is influenced by risk of recurrence, previous primary melanoma, and

family history of melanoma. Other factors, such as the presence and extent of dysplastic nevi and patient or physician concern also impact follow-up decisions (NCCN 2016). Duration of follow-up is controversial, but recurrence is highest in the first 2–5 years after treatment. Late recurrence (later than 10 years) is well documented in patients who initially present with early stage disease, but evidence is lacking to determine if frequent follow-up with these patients past the initial 5-year period is cost effective (Basseres 1995). Patients cured from a primary melanoma are at risk of at secondary melanoma and therefore should be enrolled in a more extensive surveillance program; they may benefit from total body photography. All health care professionals, including those in primary care, and family members should promote skin cancer prevention including involvement in free screening programs in the community, educational programs, and online events or live/virtual support groups.

Symptom Management

Preventing and managing drug-related toxicity is a primary role of a clinical pharmacist. The therapies used in the treatment of melanoma have varying toxicity profiles and management can be quite complex. Guidelines have been developed to assist clinicians with the management of these agents and to enable more patients to complete their full course of treatment (NCCN 2016).

Interferon continues to be an agent with complex side effects, and supportive care management can be prolonged. Toxicities such as constitutional symptoms (fever, chills, malaise), fatigue, myelosuppression, depression, and hypothyroidism are just a few of the many adverse events that patients may experience while on interferon. The development of these symptoms can range from days to weeks; therefore, appropriate follow-up is important. Flu-like symptoms and fatigue can occur within days after administration and remain for several months. Depression has a slower onset and may occur months after administration but increase in severity over time (Cancer 2008). Neutropenia and hepatic dysfunction may develop several weeks after initiation of treatment, but severity and duration remain constant over time.

Recommendations include assessing patients being treated with interferon for risk factors that may increase their likelihood for toxicity; appropriate baseline testing and assessments; and recognizing when dose reductions, ancillary drugs, or discontinuations are necessary (Hauschild 2008). Managing the dose-limiting toxicities (DLT) of interferon can be difficult. Granulocytopenia (<500 cells/m^3) or elevated liver enzymes (5 times the upper limit of normal) requires withholding the dose until resolution or less than a grade 1 side effect and then restarting with subsequent reductions based on how many previous DLT events the patient has experienced. The first DLT would result in a 33% dose reduction. A second DLT event would result in a 66% reduction, and ultimately discontinuation after the third and final episode. Dose reductions are not considered for all other potential side effects until they are considered a grade 3 or 4, at which time the dose is decreased, and the side effect is treated appropriately (Kirkwood 2002).

A risk evaluation mitigation strategy (REMS) was implemented by the FDA at the time of ipilimumab approval. The PD-1 inhibitors also have a REMS program in place that consists of a communication plan that informs health care providers of the serious risks of immunotherapy. Both ipilimumab and the PD-1 inhibitors have an immune-mediated adverse reaction management guide that can be found on the manufacturer's website that includes management guidelines of the most common side effects seen with these agent (e.g., colitis, hepatitis, rash, pneumonitis, endocrinopathies). Treatment of IRAEs associated with ipilimumab consists of holding therapy and initiating corticosteroids with a slow taper. The management of a patient with ipilimumab-induced colitis is described in Figure 2-1. In the case of endocrinopathies, thyroid medication may be initiated to maintain normal thyroid levels.

A checklist of IRAEs for nurses is essential for follow-up and requires a review with the patient at each visit. In infusion centers where electronic medical records are prevalent; a template similar to the one provided by the manufacturer can be maintained to ensure that an assessment is being completed at each treatment visit. Educating patients about their melanoma treatment and providing them with a medication card to maintain in their purse or wallet in case of an emergency is essential. Emergency contact information should also be provided to the patient should they develop one of the potential life-threatening side effects.

Side effects of PD-1 inhibitors are very similar to the IRAEs associated with ipilimumab therapy (Naidoo 2015). The side effects, however, are thought to be less toxic, and therefore more manageable. Similar treatment strategies should be used in these patients as with ipilimumab therapy, and management algorithms can also be found on the manufacturers' websites. Primary care pharmacists may be asked to assist with the treatment of side effects documented with the immunotherapies. Recognition that standard treatment for similar side effects with OTC medications (such as diarrhea) would not be appropriate and may lead to more life threatening events.

Management of toxicities associated with BRAF and MEK inhibitors differ significantly from immunotherapy management. Like most oral chemotherapy agents, the inhibitors are metabolized by the CYP system, and therefore monitoring of drug-drug interactions is one of the primary responsibilities of a clinical pharmacist. Baseline laboratory tests should be initiated to monitor for hepatotoxicity and renal dysfunction. Although the mechanisms and structures are similar, the side effect profiles vary, and therefore recognizing and distinguishing which agent is associated with each specific side effect is essential.

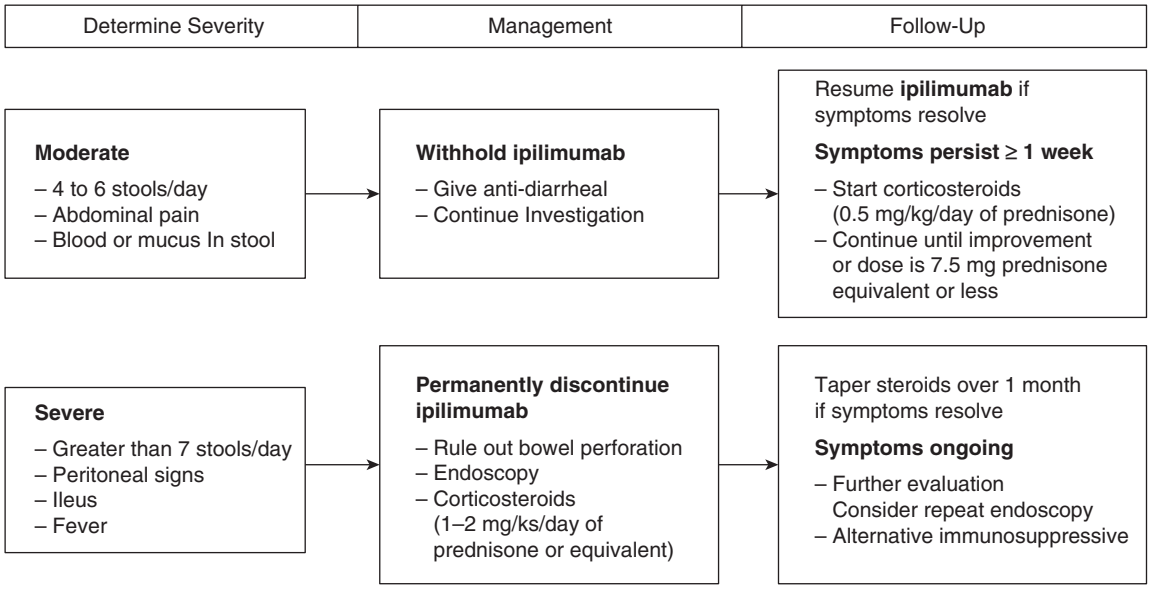

Figure 2-1. Management of ipilimumab-associated colitis.

Information from manufacturer's package insert.

Dabrafenib causes more pyrexia and GI complications; however, vemurafenib is associated with more photosensitivity, arthralgias, and hepatotoxicity. Dabrafenib should be taken without food and separated from agents that change the gastric pH. Dabrafenib should also be avoided in patients with glucose-6-phosphate dehydrogenase deficiency. Rates of hyperglycemia are higher with the use of dabrafenib than with vemurafenib. Both agents carry a risk of the development of squamous cell carcinomas and keratoacanthomas, and therefore frequent follow-up appointments with a dermatologist are recommended. Vemurafenib is associated with more cardiovascular toxicities including prolonged QTc interval. Combination BRAF and MEK inhibitor therapy cause less skin toxicity but more ocular, neutropenia, alopecia, pyrexia and fatigue, and cardiovascular adverse effects than single agent use.

CONCLUSION

Ambulatory care pharmacists have a vital role in the prevention, education, and management of melanoma. Symptom assessment, drug selection, and medication monitoring are all responsibilities that a pharmacist may have in the outpatient setting, especially for the patient on oral chemotherapy. Conducting a thorough medication history and disease state history may assist in helping with the selection of the appropriate agents both for the treatment of melanoma and for treatment-related side effects. Patient education and counseling can be extremely important in reducing adverse events and assisting with adherence. Monitoring for drug-drug interactions, especially when tyrosine kinase inhibitors are being used, remains essential to the role of a pharmacist. Pharmacists should be proactive in side effect management, assistance with adherence, and promoting safe skin protection techniques including proper clothing and sunscreen.

For localized skin cancer lesions, surgery can provide a cure. Metastatic disease has several newer treatment options but with complex side effect profiles. Appropriate initiation and titration of medications in addition to monitoring for adverse drug events should be a priority.

Practice Points

In determining the optimal treatment for a patient with melanoma:

- **Excisional biopsy with negative margins is the best chance for cure in localized melanoma.**
- **Interferon and ipilimumab improve disease-free survival as adjuvant treatment and may be used in stage III disease. Other options include a clinical trial or observation.**
- **Treatment options should be individualized based on stage, mutation analysis, disease tempo, performance status, and co-morbidities.**
- **Side effect profiles of anti-CTLA4 therapy and PD-1 inhibitors are extensive. Monitoring and toxicity management is essential.**
- **If oral therapy with a BRAF inhibitor or a BRAF/MEK inhibitor combination is warranted, laboratory monitoring and drug-drug interaction screening is recommended.**
- **Adherence monitoring is an opportunity for clinical pharmacists to assist with improving outcomes and decreasing side effects.**

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Self-Assessment Questions

22. A 52-year-old white man is referred to an oncologist for a suspicious ulcerated lesion on his right shoulder that continues to grow. His family history includes familial atypical multiple mole syndrome; his father died of cutaneous melanoma at the age of 61. Physical examination reveals a blonde-headed, medium-skinned, green-eyed man with a dark black, 1.2-cm suspicious lesion that is ulcerated on the right shoulder blade. Which of the following genes or gene mutations is most likely to have increased this patient's risk of developing melanoma?

    A. CDKN2A
    B. BRAF
    C. BRCA2
    D. MCIR

23. A comprehensive meta-analysis was conducted to determine relative risks for sun exposure patterns and the association of melanoma.

Sun Exposure	Relative Risk	95% CI
Intermittent	2.35	(1.8–3.1)
Chronic	1.3	(0.7–0.9)

    Based on these data, which one of the following best describes how intermittent sun exposure compares with chronic sun exposure?

    A. Intermittent sun exposure is 2 times as likely to cause melanoma than chronic exposure
    B. Intermittent sun exposure has less risk for melanoma than chronic sun exposure
    C. Chronic exposure is 2 times as likely to cause melanoma than intermittent exposure
    D. Chronic exposure does not increase you risk of melanoma

Questions 24 and 25 pertain to the following case.

K.T. is a 41-year-old white woman who presents to her first appointment with her dermatologist. Physical examination reveals a woman with red hair, green eyes, and freckling, together with multiple moles on her arms, chest, and back. K.T.'s medical history includes removal of two dysplastic nevi 5 years ago.

24. According to the American Academy of Dermatology (AAD), which screening program is best to recommend for K.T.?

    A. She should undergo screening photography every 6 months.
    B. She should perform monthly self-examinations and see a dermatologist for any changes in moles or marks.
    C. She needs no visual cancer screening, including self-examinations.
    D. She should have annual clinical examination by a dermatologist and perform monthly self-examinations.

25. K.T.'s dermatologist suggest she wear a sunscreen daily with maximum UV protection along with protective clothing to decrease her risk of skin cancer. According to the most recent AAD recommendations, which one of the following sunscreens is best to recommend for K.T.?

    A. SPF of 15 and UVA protection
    B. SPF of 15 and UVA and UVB protection
    C. SPF of 30 and UVB protection
    D. SPF of 30 and UVA and UVB protection

26. A 35-year-old white man was recently seen by a dermatologist after he noticed a mole on his right foot was changing in color and size. His social history is significant for sun exposure while he worked as a lifeguard for several summers during college. His medical history is significant for depression. Physical examination reveals a blonde-haired, blue-eyed, medium-skinned man with a 2-cm mole. The patient complains of this lesion itching and being scaly. An excisional biopsy of the lesion reveals a superficial spreading melanoma ulcerated lesion with a 2.6 mm thickness and a mitosis rate of 1 mm^2. Sentinel lymph node biopsy was negative and margins were negative. Which one of the following is best to recommend for this patient?

    A. Observation alone
    B. Clinical trial or observation
    C. Clinical trial or observation or interferon
    D. Clinical trial, observation, or ipilimumab

27. A 25-year-old white woman who is in her third year of pharmacy school presents to the cancer center to see an oncologist for the first time since the excisional removal of her T4aN1aM0 melanoma lesion. Her surgeon wants her to discuss adjuvant treatment options with her oncologist. The patient is convinced that she would like to initiate interferon therapy. Which one of the following is best to recommend for this patient?

    A. Low-dose interferon treatment for 1 year
    B. Intermediate-dose interferon for 1 year
    C. High-dose interferon for 1 year
    D. Pegylated interferon for 1 year

28. A double-blind, phase III trial was conducted in patients with previously untreated, lymph node resected, stage III cutaneous melanoma. Patients received either

ipilimumab 10 mg/kg or placebo every 3 weeks for four doses, then every 3 months for up to 3 years. At a median follow-up of 2.74 years, the median recurrence-free survival was 26.1 months in the ipilimumab group versus 17.1 months in the placebo group (HR 0.75; 95% CI, 0.64–0.90; p=0.0013). Which one of the following best interprets these data regarding ipilimumab?

A. It has similar rates of recurrence free survival and is considered as good as placebo.
B. It has a statistically significant decrease in recurrence free survival as compared with placebo.
C. The difference in recurrence-free survival versus placebo was statistically significant but not clinically significant.
D. It reduces the hazard of death by 15% compared with the placebo group.

29. A 57-year-old man with newly diagnosed metastatic melanoma presents to the ambulatory care clinic after his first treatment with pembrolizumab. When asked if he understands the side effects of his new drug, he is unable to verbalize any information. Which one of the following adverse effects is it best to educate this patient about?

A. Depression
B. Flu-like symptoms
C. Neutropenia
D. Pneumonitis

30. A 72-year-old man recently received a diagnosis of T2N1M1 melanoma. His pathology reported negative margins, one positive sentinel lymph node, and wild-type BRAF. His performance status is an ECOG of 1. The patient has no other comorbidities and is eager to initiate systemic treatment. Which one of the following is best to recommend for this patient?

A. Dabrafenib and trametinib
B. High-dose interleukin-2
C. Biochemotherapy
D. Nivolumab

31. A 61-year-old man with newly diagnosed metastatic melanoma presents to his oncologist for the first time after surgery. His medical history is significant for hypertension and diabetes. Based on imaging, the oncologist discloses to the patient that he has bulky disease, the tumor is rapidly progressing, and his tumor has a BRAF V600E mutation. Which one of the following is best to recommend for this patient?

A. Dacarbazine
B. Ipilimumab
C. Dabrafenib and trametinib
D. High-dose interleukin-2

Questions 32 and 33 pertain to the following case.

V.M. is a 28-year-old woman who recently received a diagnosis of stage III melanoma (T1N1M0). After hearing the risk versus benefit of initiating adjuvant therapy, she has decided to try interferon. She is receiving 6 mg/kg of pegylated interferon subcutaneously for up to 5 years. Her medical history is significant for depression. V.M. does not have any active drugs on her medication profile and she denies taking any OTC products. She is back in the clinical pharmacy clinic today for her follow-up laboratory tests at 30 days.

32. V.M.'s laboratory tests today reveal an AST of 350 and an ALT of 400. Which one of the following is best to recommend for V.M.?

A. Discontinue therapy.
B. Hold therapy until resolution and then reduce dose by 66% from initial dose.
C. Hold therapy until resolution and then reduce dose by 33% from initial dose.
D. Hold therapy until resolution and then reinitiate at initial dose.

33. V.M. returns for her 3-month check-up and reveals that she is more fatigued, has less motivation, and spends a lot of time alone. Her laboratory values today are within normal limits. Which one of the following is best to recommend for V.M.?

A. Discontinue therapy.
B. Hold therapy and consider dose reduction.
C. Administer a HAM-D depression screen and consult a psychiatrist.
D. Hold therapy and resume treatment at the same dose once the effects disappear.

Questions 34 and 35 pertain to the following case.

L.S. is a 54-year-old woman with stage IIIC melanoma (BRAF wild-type) who was initiated on ipilimumab. She presents to the clinic today for her third dose. A nursing side effect checklist was reviewed, and L.S. denied having any side effects or toxicity from ipilimumab thus far. She was without issues during her infusion and left in no apparent distress. Twenty-four hours later, L.S. presents to the ED reporting at least 8 episodes of diarrhea

34. L.S. is admitted to the hospital with a fever and continued episodes of diarrhea, and intravenous fluids are initiated. Which one of the following is best to recommend for L.C.'s diarrhea?

A. Intravenous fluids
B. Diphenoxylate/atropine
C. Prednisone
D. Loperamide

35. L.S. is getting ready to be discharged from the hospital. She is afebrile and her symptoms are resolving. While providing discharge counseling, she asks when she can resume her treatment. Which one of the following is the best recommendation for L.S.?

    A. She can resume ipilimumab at the same dose if her symptoms resolve.
    B. She can resume ipilimumab at 25% of the same dose if her symptoms resolve.
    C. She can resume ipilimumab at 50% of the same dose if her symptoms resolve.
    D. She can never resume ipilimumab.

36. Six years ago, a 45-year-old woman received a diagnosis of melanoma (T2N1M0) and underwent 5 years of pegylated interferon. Recently, she has been short of breath, has difficulty going up and down the steps at work, and is no longer able to go to the gym 4 days a week. She presents to her oncologist's office after a CT scan reveals a lesion in her left upper lobe, followed by a biopsy confirming recurrent melanoma. The biopsy also reveals that her melanoma is BRAF wild-type. Which one of the following therapies is most likely to give this patient the best progression-free survival?

    A. Ipilimumab
    B. Ipilimumab and nivolumab
    C. Interleukin-2
    D. Dabrafenib and trametinib

37. A 26-year-old woman with stage IV metastatic melanoma has been on dabrafenib and trametinib therapy for 2 weeks. She is scheduled for follow-up with the clinical pharmacist to talk about adherence and to review side effects and today's blood work. Upon review of her chart, you notice she has a medical history significant for generalized anxiety disorder and gastroesophageal reflux disease. Her drugs include lorazepam 0.5 mg three times a day as needed, omeprazole 40 mg daily, ondansetron 8 mg three times a day as needed, and ethinyl estradiol/norgestimate daily. Which one of the following is most likely to contribute to a drug-drug interaction with this patient's dabrafenib and trametinib therapy?

    A. Lorazepam
    B. Omeprazole
    C. Ondansetron
    D. Ethinyl estradiol/norgestimate

38. A 69-year-old man with unresectable melanoma presents to clinic after seeing some advertisements on television about a new intralesional virus therapy for melanoma. His medical history includes hypertension, hypothyroidism, GERD, and recurrent shingles. The patient's home drugs include hydrochlorothiazide 25 mg, levothyroxine 0.1 mg daily, valacyclovir 500 mg twice daily, and omeprazole 40 mg daily. The oncologist has agreed to initiate talimogene laherparepvec in 2 weeks. As the clinical pharmacist, you are reviewing his medication list and notice there could be a drug-drug interaction with one of his current medications. Which one of the following is best to recommend for discontinuation while this patient is on the new treatment?

    A. Hydrochlorothiazide
    B. Levothyroxine
    C. Valacyclovir
    D. Omeprazole

39. A 36-year-old woman with metastatic melanoma just completed a 9-month treatment course of therapy with ipilimumab and nivolumab. She tolerated treatment, but her latest imaging revealed a new metastatic brain lesion. Her social history includes being a physical education instructor and is outside with her students multiple days a week. Her biopsy revealed her tumor has a BRAF mutation and she is interested in trying an oral therapy with the least amount of side effects, and to attempt to improve her quality of life. Which one of the following is best to recommend for this patient?

    A. Vemurafenib and trametinib
    B. Cobimetinib
    C. Dabrafenib and trametinib
    D. Trametinib

40. A 59-year-old man who has metastatic melanoma presents to the clinic to discuss potential treatment options. His most recent scan reveals that he now has multiple brain lesions and a lung lesion. He claims that he still feels good and would like to pursue additional treatment. His ECOG performance status is a 1. His previous therapies include nivolumab plus ipilimumab combination therapy, dabrafenib plus trametinib, and pembrolizumab single agent therapy. Which one of the following is best to recommend for this patient?

    A. Clinical trial
    B. Carboplatin and paclitaxel
    C. Interleukin-2
    D. Talimogene laherparepvec

41. A 50-year-old woman with cutaneous melanoma was recently enrolled in a clinical trial for her T2N1M0 disease. The clinical trial includes interferon versus a new vaccine. She is concerned about potential side effects from high-dose interferon. She is a nurse and does not want to take any additional time off work. Her medical history is significant for hypertension, diabetes, and hypothyroidism. Which one of the following side effects is most important to monitor for in this patient?

    A. Constipation
    B. Neutropenia
    C. Sun sensitivity
    D. Cardiac toxicity

Learner Chapter Evaluation: Melanoma.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Demonstrate an understanding of the epidemiology of melanoma skin cancers and the role of screening for the prevention of skin cancer.
31. Evaluate the role of immunotherapy in the adjuvant treatment of melanoma.
32. Evaluate the role of ipilimumab, nivolumab, and pembrolizumab in the treatment of metastatic melanoma.
33. Justify the role of genetic analysis in treatment selection with BRAF/MEK tyrosine kinase inhibitors.
34. Distinguish the role of oral BRAF inhibitor therapy in the treatment of skin cancer.
35. Design pharmacotherapy – including monitoring parameters, side effect management, and, where applicable, oncolytic virus therapy – for the patient with metastatic melanoma

Questions 36–38 apply to the entire learning module.

36. How long did it take you to read the instructional materials in this module?
37. How long did it take you to read and answer the assessment questions in this module?
38. Please provide any additional comments you may have regarding this module:

Oncologic Care III

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Cancer Survivorship

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Cancer Survivorship

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LEARNING OBJECTIVES

1. Compose an appropriate management plan for a cancer survivor with treatment-induced cardiotoxicity.
2. Evaluate the pharmacologic and nonpharmacologic options for managing peripheral and central neurotoxicities.
3. Develop a treatment plan to manage cancer-related fatigue and sleep disorders in cancer survivors.
4. Compose recommendations associated with sexual health and infertility in cancer survivors.
5. Apply screening and lifestyle recommendations to individualize care in cancer survivors.
6. Justify the importance of implementing a survivorship care plan.

ABBREVIATIONS IN THIS CHAPTER

ASCO	American Society of Clinical Oncology
CBT	Cognitive behavioral therapy
CIPN	Chemotherapy-induced peripheral neuropathy
CRF	Cancer-related fatigue
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CVD	Cardiovascular disease
ED	Erectile dysfunction
HF	Heart failure
HSCT	Hematopoietic stem cell transplantation
LVD	Left ventricular dysfunction
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRT	Nicotine replacement therapy
PDE5	Phosphodiesterase type 5

Table of other common abbreviations.

INTRODUCTION

Definition of Cancer Survivorship

With medical advances and the success of cancer screening and treatment, cancer mortality has dramatically declined over the past 2 decades. Accordingly, this has led to a growing number of cancer survivors. The National Cancer Institute (NCI) has adopted the definition of a cancer survivor from the National Coalition for Cancer Survivorship. An individual is defined as a cancer survivor "from the time of diagnosis through the balance of his or her life." The definition also includes family members, friends, and caregivers who are affected by the survivorship experience (Office of Cancer Survivorship 2014). However, the functional definition of survivorship, which is well accepted in the oncology community, focuses on individuals who have successfully completed curative treatments or transitioned to maintenance or prophylactic therapy (McCabe 2013).

Prevalence and Survivorship Trajectory

In the United States, it is estimated that 15.5 million people were given a diagnosis of cancer in 2012, which is a 4-fold increase compared with 1975 (Bluethmann 2016; de Moor 2013). The number of survivors is expected to increase to 18 million over the next decade. The largest relative increase in cancer survivors will be in those who have survived more than 15 years after their diagnosis (de Moor 2013). The most prevalent cancer survivors include those who have survived breast cancer (22%), prostate cancer (20%), and colorectal cancer (9%) (de Moor 2013).

COMMON PHYSICAL AND PSYCHOSOCIAL PROBLEMS

Although the consequences of cancer are generally minimal and most patients can return to a normal life after completing curative treatment, many cancer survivors have physical and psychosocial problems from the cancer and its treatment. Some of these problems may occur while patients are receiving treatment, and some can appear just months or years after active therapy. Many epidemiological studies have evaluated the health problems seen in different populations of cancer survivors.

Adult Cancer Survivors

One of the largest studies evaluating health status in adult cancer survivors was conducted by the U.S. National Health Interview Survey in 2010 (Weaver 2012). A total of 1882 cancer survivors and 24,804 adults without a cancer diagnosis were surveyed. Survey participants were assessed using the Patient-Reported Outcomes Measurement Information System Global Health Scale for their physical and mental health–related quality of life. Poor physical or mental health was defined as an individual having a physical or mental health score 1 SD below the U.S. population mean. In this study, most survivors were 65–79 years old, white, were women, and had at least two comorbidities. Among the adults without a cancer diagnosis, the prevalence of poor physical health was 10.9%, whereas that of cancer survivors was 24.5%. Similarly, the prevalence of poor mental health was 5.9% among adults without a cancer diagnosis and 10.1% among cancer survivors. This study also identified participants at a higher risk of physical and mental health issues. Survivors who were less well educated and had more than one non-cancer comorbidity were at risk of poor physical health. However, survivors who were young, unmarried, and less well educated and had several comorbidities were at a greater risk of poor mental health.

Pediatric Cancer Survivors

The Childhood Cancer Survivor Study investigated the health problems in a cohort of adults who had survived for at least 5 years after treatment for childhood cancer (Oeffinger 2006). The incidence of health issues was compared between 10,397 cancer survivors and 3034 nearest-age living siblings. Among the survivors, 62.3% reported having at least one chronic health condition, with 27.5% reporting a grade 3 (severe) or grade 4 (life-threatening or disabling) condition. In contrast, among siblings, 36.8% reported having a chronic health condition, of whom 5.2% reported having a grade 3 or 4 condition. After adjustment for age, sex, and race, survivors were 3.3 times as likely as their siblings to have a chronic health condition of any grade (95% CI, 3.0–3.5).

Comparing the incidence of health conditions between survivors and siblings, the following five severe conditions were more likely among survivors: major joint replacement (RR 54.0; 95% CI, 7.6–386.3), congestive heart failure (HF) (RR 15.1; 95% CI, 4.8–47.9), second malignancy (RR 14.8; 95% CI, 7.2–30.4), severe cognitive dysfunction (RR 10.5; 95% CI, 2.6–43.0), and coronary artery disease (RR 10.4; 95% CI, 4.1–25.9). Furthermore, exposure to one of five of the following treatment combinations was associated with a very high risk of having a grade 3 or 4 chronic health condition: chest radiation plus bleomycin, chest radiation plus an anthracycline, chest radiation plus abdominal or pelvic irradiation, receipt of anthracycline together with an alkylating agent, and abdominal or pelvic irradiation in combination with an alkylating agent.

Survivors of Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplants (HSCTs) are used as a curative treatment option for several types of hematological malignancies. With the improvement in patient selection, transplant strategies, and supportive care options, an increasing number of individuals with hematological malignancies become long-term HSCT survivors. In one study that evaluated the long-term morbidities among HSCT survivors, the incidence of survivors' health conditions was compared against that of their sibling controls (Sun 2013). Compared with their siblings, HSCT survivors were 2.2 times more likely to report a grade 1–4 condition (95% CI, 1.8–2.5, p<0.001) and 5.7 times more likely to report a severe/life-threatening condition (95% CI, 3.8–8.7, p<0.001). Although recipients of autologous HSCT were more likely to report coronary artery disease,

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge on management of various cancers
- Pharmacologic management of heart failure
- Pharmacologic management of erectile dysfunction

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- National Comprehensive Cancer Network [homepage on the Internet].
- Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure. J Am Coll Cardiol 2013;62:e147-239.
- American Urological Association. The Management of Erectile Dysfunction [homepage on the Internet].

significant hearing loss, and second malignancies, recipients of allogeneic HSCT were more likely to report a stroke, significant visual impairment, hepatic cirrhosis, diabetes, and osteonecrosis necessitating joint replacements. Survivors of HSCT were also 2.7 times more likely to report emotional distress because of physical symptoms than their sibling controls.

CARDIAC TOXICITIES

Many anticancer therapies can lead to short- and long-term cardiotoxicities, including left ventricular dysfunction (LVD), HF, hypertension, ischemia, and rhythm disorders. Among the cardiotoxicities associated with cancer treatment, LVD and HF are the most common manifestations of anticancer therapy cardiotoxicities.

Clinical Presentation and Risk Factors

Some investigators have classified anticancer treatment–associated cardiotoxicity on the basis of structural abnormalities and extent of reversibility (Suter 2013). Patients with type I cardiotoxicity have signs and symptoms characterized by dose-cumulative and irreversible myocardial damage. Certain drugs, including anthracyclines (e.g., doxorubicin), mitoxantrone, and cyclophosphamide, are often associated with type I cardiotoxicity. Although acute cardiotoxicity caused by anthracycline-related LVD is rare, the chronic form can occur in 4%–5% of patients as many as 15–20 years later (Green 2001; Kremer 2001). Most anthracycline cardiotoxicity occurs in the first year. The lifetime doxorubicin limit is 400–550 mg/m^2, or an alternative equivalent is recommended because a cumulative dose is the main predictor of anthracycline cardiotoxicity (Swain 2003). However, variability in anthracycline tolerance exists because some patients develop irreversible cardiotoxicity at low doses, whereas others can tolerate amounts above the maximum recommended dose. Characteristics such as older age, female sex, prior/concurrent chest radiation, low-normal ejection fraction (50%–55%), concomitant cardiotoxic therapies, and preexisting cardiovascular disease (CVD) increase cardiotoxicity risks. To maximize anthracycline efficacy and tolerability, cardiovascular (CV) risk factors should be optimized and treated, if present.

Type II cardiotoxicity, however, is not dose-dependent and is potentially reversible on drug discontinuation. Targeted therapies such as trastuzumab are associated with this type of cardiotoxicity. However, this classification is not mutually exclusive because trastuzumab can also trigger irreversible cardiac damage in patients with severe cardiac disease. Trastuzumab exposure is associated with a 9.8% incidence of LVD and severe cardiomyopathy in 2.7% of patients, with most cardiac events occurring within 18 months of initial exposure (Bowles 2012). Patients 50 and older with underlying heart disease, hypertension, and baseline left ventricular ejection fraction less than 55% have higher risks (Curigliano 2016). Coadministration of anthracyclines such as doxorubicin may increase the risk of type II cardiotoxicity.

Prevalence

Survivors of childhood cancer, including leukemia, CNS malignancies, and Hodgkin lymphoma, have a 10- and 15-fold increased risk of developing CVD and HF, respectively, and a 7-fold increased risk of CV-related death compared with age-matched peers (Mertens 2008; Oeffinger 2006). Cardiac radiation and cumulative anthracycline exposure were significant risk factors for cardiac-related death (Mertens 2008). Among patients with breast cancer who are older than 50, CVD was the predominant cause of mortality. Incidental cardiac exposure to radiation during breast cancer radiotherapy increased the rate of major coronary events by 7.4% per gray of radiation within the first 5 years after exposure and continues into the third decade after radiotherapy (Darby 2013). Incidence of HF is relatively low (0.2%–0.9%) when doxorubicin is used as part of an adjuvant chemotherapy regimen for breast cancer because cumulative doses generally do not exceed 240 mg/m^2 (Shapiro 2001). However, doxorubicin-induced HF rates increase dramatically from 4.7% to 26% at cumulative doses of 400 mg/m^2 and 550 mg/m^2, respectively (Swain 2003). This emphasizes that early recognition and treatment of cardiac complications in patients with cancer or who survive cancer is essential.

Current Management

Detection and Monitoring

Before treatment, it is important to evaluate baseline left ventricular ejection fraction, ECG, and cardiac structure and function assessments. Measurement of left ventricular ejection fraction is a widely accepted cardiac function parameter that predicts CV event mortality, but it is not sensitive enough to detect early cardiotoxicity. The National Comprehensive Cancer Network (NCCN) survivorship guidelines suggest that survivors with one or more CV risk factors who have completed anthracycline therapy should be assessed with cardiac imaging within 12 months of the last anthracycline dose.

Alternative measures of cardiac function have been explored, where an increase in cardiac biomarkers (troponins and brain natriuretic peptide concentrations, in particular) may identify patients with early cardiac damage. Troponin measurements at baseline and after each anthracycline or trastuzumab cycle can identify patients needing further cardiac assessment, but optimal surveillance strategies have not been defined.

The American College of Cardiology Foundation/American Heart Association guidelines for the evaluation and management of heart failure are commonly used to classify the stages of HF (Yancy 2013). Asymptomatic individuals are classified as having stage A. Individuals are classified as having stage B if they are at risk of HF or have structural abnormalities of the heart, whereas individuals are classified as having stage C HF when clinical signs and symptoms accompany structural changes to the heart. Stage D is classified

as the most advanced stage, with patients having advanced structural disease and significant HF symptoms at rest that are refractory to medical therapy.

Pharmacologic Interventions

Before initiating cardiotoxic chemotherapy, clinicians should impose aggressive control of patients' CV risk factors or related comorbidities and treatment optimization of preexisting cardiopathies. Early recognition of cardiotoxicity at treatment initiation potentially increased the chances of cardiac recovery in limited studies investigating cardioprotective agents including dexrazoxane and primary and secondary prophylaxis with angiotensin-converting enzyme inhibitors (ACEIs) and β-blockers (Kalam 2013). Dexrazoxane is approved as a cardioprotectant, and the American Society of Clinical Oncology (ASCO) recommends its use in patients with metastatic cancer who have received over 300 mg/m^2 of doxorubicin (Hensley 2009). Prevention of cardiomyopathies and HF development by angiotensin system blockade with ACEIs or angiotensin receptor blockers (ARBs) and β-blockers in patients newly initiated on anthracycline-containing regimens has been studied with valsartan, carvedilol, and a combination of titrated enalapril and carvedilol. A meta-analysis of various cancers (hematologic, breast, and sarcoma) had 69% and 89% risk reductions in cardiac events with prophylactic β-blockers and ACEI or ARB use, respectively (Kalam 2013). However, not all agents are deemed equally effective. Currently, HF prevention using prophylactic β-blockers, ACEIs, or ARBs should only be done in a clinical trial setting.

The NCCN guidelines recommend that all survivors with exposure to anthracyclines have stage A HF and should be treated through reduction in risk factors. Risk factors such as hypertension, obesity, metabolic syndrome, and diabetes must be addressed. In addition, these survivors should engage in regular physical activity, dietary control, and avoiding behaviors that may aggravate the risk of HF or CVD.

In survivors with stage B, C, or D HF, the sooner treatment is initiated, the more likely it is to be successful (Cardinale 2010). Management of HF should follow the guideline recommendations provided by the American College of Cardiology Foundation/American Heart Association (Yancy 2013). Although data regarding medical therapy for cancer survivors with symptomatic LVD are limited, HF therapy, including ACEI or ARB and β-blocker therapy, should be initiated to reduce morbidity and mortality. Trastuzumab-induced cardiotoxicity in patients with breast cancer is generally reversible after discontinuation. However, certain patients may require initiation of standard medical therapy.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating toxicity of several cytotoxic agents, including antimicrotubule agents (e.g., taxanes and epothilone analogs), platinum agents, bortezomib, thalidomide, lenalidomide, and vinca alkaloids (Table 1-1). Chemotherapy-induced peripheral neuropathy causes significant distress in patients with cancer and cancer survivors and can be associated with decreased quality of life, reduced functional ability, and increased risk of falls; it has also been associated with increased health care use such as using prescription and OTC medications for pain relief (Reyes-Gibby 2009).

Clinical Presentation and Risk Factors

Chemotherapy-induced peripheral neuropathy often presents as a sensory neuropathy characterized by numbness, tingling, and pain, which generally starts in the fingers and toes and spreads proximally in a "stocking-glove" distribution. Chemotherapy-induced peripheral neuropathy symptoms predominantly consist of sensory rather than motor symptoms. Symptom severity is also dose-dependent, and symptoms become progressively worse during treatment. The likelihood of neuropathy is higher in patients who have another contributing predisposition for neuropathy such as diabetes mellitus, obesity, and older age.

Prevalence

In general, CIPN improves after treatment is completed. However, lingering symptoms may persist in many survivors over a long period. With oxaliplatin, it was reported that the symptoms are partly reversible in about 80% of survivors. The symptoms are completely resolved in about 40% of patients at 6–8 months after treatment cessation (Argyriou 2012). However, signs and symptoms may continue to develop and progress for 2–6 months after treatment has ended, a phenomenon known as "coasting." Taxane-induced peripheral neuropathy may also improve in most cancer survivors in the months after ending treatment. However, symptoms may continue to be prominent over a long period in a subset of patients (Reyes-Gibby 2009). Vinca alkaloids such as vincristine and vinblastine may also increase a survivor's risk of neuropathy. Survivors of childhood acute lymphocytic leukemia and multiple myeloma often have long-lasting peripheral neuropathy caused by frequent exposure to vincristine during their treatment (Jain 2014; Boland 2013).

Current Management

Screening and Assessment

There are no standardized approaches to assess CIPN. The National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03) is the most commonly used system by clinicians to grade the severity of neuropathy symptoms. However, clinician-based assessments are often criticized because they may underestimate the significance of symptoms compared with patient reports. Hence, other measures such as an objective neurophysiological assessment and symptom assessment using

Table 1-1. Anticancer Agents Associated with Peripheral Neuropathy

Drug(s)	Sensory Neuropathy	Motor Neuropathy	Autonomic Neuropathy
Bortezomib	Painful, small-fiber sensory neuropathy	Rare	Yes
Brentuximab vedotin	Sensory neuropathy	Weakness in extremities	Rare
Carboplatin	Predominantly sensory neuropathy	Rare	Rare
Cisplatin	Predominantly sensory neuropathy	Rare	Rare
Docetaxel	Predominantly sensory neuropathy	At higher doses, myalgia and myopathy	Rare
Eribulin	Sensory neuropathy	Myopathy or foot drop	Rare
Ixabepilone	Sensory neuropathy	Myopathy or foot drop	Rare
Oxaliplatin	Acute sensory symptoms and chronic sensory neuropathy	Acute cramps and fasciculations	Rare
Paclitaxel	Predominantly sensory neuropathy	At higher doses, myalgia and myopathy	Rare
Thalidomide	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes
Vincristine	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes (constipation)
Vinblastine	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes
Vinorelbine	Sensory neuropathy	Muscle cramps and mild distal weakness	Yes

patient-reported outcomes tools are now commonly used in clinical practice for CIPN assessment. The gold standard for the objective neurophysiological assessment of CIPN involves using nerve conduction studies, which measure the amplitude and conduction velocity of compound sensory action potentials and compound motor action potentials. For patient-reported outcomes, several tools (e.g., the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity) have been developed to capture the impact of neuropathy symptoms on health-related quality of life (Table 1-2).

Nonpharmacologic Intervention

Scrambler therapy, a patient-specific electrocutaneous nerve stimulation device, is currently under investigation for the management of CIPN. It provides some benefit in reducing neuropathic pain in patients with cancer. Scrambler therapy is given once daily over 1–2 weeks. It stimulates the nerves and provides a non-pain stimulus to block the pain sensation from the affected area.

Pharmacologic Interventions

In 2014, the ASCO published practice guidelines for the management of CIPN in survivors of adult cancers (Hershman 2014). The guidelines are primarily derived from randomized controlled studies that evaluated the role of pharmacologic agents for the management of CIPN. The guidelines recommend using duloxetine for the treatment of CIPN with moderate confidence (Hershman 2014). One phase III randomized controlled trial evaluated duloxetine (target dose of 60 mg daily) for the treatment of painful CIPN attributed to prior taxane or oxaliplatin therapy (Smith 2013). Patients who received duloxetine had a statistically significant larger average reduction in pain score than those receiving placebo, with a moderate effect size. Results from a subgroup analysis also suggest that duloxetine is more efficacious for oxaliplatin-induced, versus paclitaxel-induced, CIPN.

Opioids, a class of agents commonly used for the treatment of chronic pain, are effective for treating a variety of forms of neuropathic pain. However, they are often recommended as second- or third-line treatments in various consensus statements.

The ASCO recommendations for using other pharmacologic agents, including acetyl-L-carnitine, gabapentin, tricyclic antidepressants (amitriptyline and nortriptyline), and topical gel (combination of amitriptyline, ketamine, and baclofen), are inconclusive, suggesting that evidence of effectiveness is conflicting and further research is needed. Although many of these agents such as tricyclic antidepressants and gabapentin are commonly used in practice, few well-designed studies show their effectiveness. The guidelines also recommend against lamotrigine use for the treatment of established CIPN. Because of the limited treatment options available for managing CIPN, the guidelines suggest

Table 1-2. Assessment of Chemotherapy-Induced Peripheral Neuropathy

Assessment Tools	Mode of Assessment	Description of Assessment	Grading
Subjective Assessment			
National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 4.03)	Clinician assessed	Assess sensory neuropathy, motor neuropathy, dysesthesia, neuralgia, and paresthesia	Grades 0–5
Patient Neurotoxicity Questionnaire (PNQ)	Clinician assessed	Two items; assess sensory and motor symptoms and how symptoms interfere daily activities	Grades A–E
Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (Fact/GOG-Ntx) version 4.0	Patient-reported outcomes	38 items to capture how neuropathic symptoms have affected quality of life over the past 7 days	5-level Likert scale
European Organisation for Research and Treatment of Cancer-Quality of Life-Chemotherapy-Induced Peripheral Neuropathy-20 (EORTC QLQ-CIPN-20)	Patient-reported outcomes	20 items; focus on sensory, motor, and autonomic neuropathy	4-level Likert scale
Objective Assessment			
Nerve conduction studies	Clinician assessed	A medical diagnostic test; measurement of electrical conduction of nerve impulses	Quantitative measures

that patients should be informed of the limited scientific evidence of these agents for managing CIPN and that potential harms, benefits, cost, and preferences related to these agents should be discussed with them.

CANCER-ASSOCIATED COGNITIVE CHANGES

Alterations in cognitive function often occur in patients receiving chemotherapy, particularly in those treated for breast cancer. In the literature, this phenomenon is known as "chemobrain" or "chemo fog." The etiology behind cognitive impairment after chemotherapy is currently unknown. However, many factors have been postulated as determinants of cognitive changes in patients with cancer, including demographic, physiological, psychological, pathological, and pharmacologic determinants. Recent studies have suggested that proinflammatory cytokines (e.g., interleukin [IL]-6 and IL-1β) are mediators of chemotherapy-associated cognitive changes (Cheung 2015). Cytokine induction in the CNS has been suggested to give rise to a cluster of cancer-related symptoms including fatigue, depression, and stress, which are also associated with cognitive changes (Cheung 2013).

Clinical Presentation and Risk Factors

Cognitive changes can include poor word or name recall, difficulty staying focused, diminished ability to learn new things, and decreased ability to multitask. Other alterations in executive function, information processing speed, language, motor function, and spatial skills have also been reported. Depending on the nature of the malignancy and the treatment regimen, the onset, severity, and duration of these changes are variable, as are its effects and functional and psychosocial outcomes. Patients receiving several types of cytotoxic treatment in combination are at a higher risk of developing cognitive impairment after treatment (Cheung 2012). Other characteristics such as older age, carriers of genetic polymorphism (e.g., apolipoprotein E or brain-derived neurotrophic factor), postmenopause, high educational level, and severe psychological distress may affect a cancer survivor's risk of cognitive changes (Cheung 2013).

Prevalence

Depending on the type of cancer investigated, estimates of the prevalence of cancer-related alterations in cognitive function are 16%–75% during treatment, although these changes can remain after completion or withdrawal of treatment (Cheung 2012). Neuroimaging studies have revealed a correlation between deficits in cognitive function and white matter changes in the brain. Supported by findings from neuropsychological tests, reports indicate that individuals can still have cognitive changes for as long as 20 years after chemotherapy for breast cancer (Koppelmans 2012).

Patient Care Scenario

A 58-year-old man with a history of colon cancer presents at the survivorship clinic. He has recently completed his adjuvant therapy with fluorouracil and oxaliplatin. On review of systems, he has complaints of numbness and tingling in his fingers, and the symptoms affect him greatly during his daily activity. He cannot dress and undress himself without sharp pain in his fingers. Furthermore, his symptoms are exacerbated whenever he touches cold objects. Nerve conduction studies suggest axonal loss and demyelination of sensory, median, and ulnar nerves.

Before his cancer diagnosis, the patient had a medical history of diabetes and peripheral neuropathy, and he had used oxycodone intermittently to control his pain. The oncologist believes that the patient has chronic peripheral neuropathy exacerbated by his recent use of oxaliplatin. What pharmacologic agent would be best to recommend to this patient?

ANSWER

Chemotherapy-induced peripheral neuropathy is a cause of significant distress in patients with cancer and is associated with decreased quality of life and functional disability. This patient describes classic signs and symptoms of oxaliplatin-induced peripheral neuropathy – numbness and tingling in his fingers – and the symptoms are severe enough that they are affecting his daily activities (according to NCI-CTCAE version 4.03, his symptoms are grade 3). On objective nerve conduction studies, several abnormalities are detected, which include axonal loss (refers to lower nerve amplitudes) and demyelination (refers to prolonged latency and slow conduction velocity). Furthermore, the patient's symptoms are exacerbated because of diabetic neuropathy.

For treatment of his neuropathy, duloxetine is useful and is also indicated for the treatment of diabetic neuropathy. In addition to a randomized control trial that showed its efficacy in managing CIPN, three randomized controlled clinical trials that investigated duloxetine for the treatment of diabetic peripheral neuropathic pain had positive results at a dosage of 60 mg daily, with 120 mg/day providing no further benefit. Duloxetine is currently considered a first-line treatment of non-CIPN neuropathic pain and is FDA approved for the treatment of painful diabetic neuropathy.

Opioids are generally recommended as second- or third-line treatments of non-CIPN neuropathic pain in various consensus statements. Randomized controlled trials have shown the efficacy of controlled-release oxycodone in the treatment of diabetic neuropathy. Tapentadol was recently FDA label approved for the treatment of painful diabetic neuropathy. Data are limited specifically evaluating the effect of opioids for the treatment of CIPN. One trial investigated the combination of tramadol and acetaminophen for the treatment of oxaliplatin-induced CIPN. Ninety-six patients with oxaliplatin-induced CIPN received tramadol/acetaminophen 1 tablet every 6 hours. Unfortunately, there was no significant improvement.

1. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2014;32:1941-67.
2. Smith EM, Pang H, Cirrincione C, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA 2013;309:1359-67.

Current Management

Screening and Assessment

Survivors reporting cognitive changes should be screened for potentially reversible factors that may contribute to cognitive changes, which include psychological distress, fatigue, sleep disturbances, and pain. Medications that affect neurological function such as benzodiazepines and corticosteroids can also contribute to cognitive changes; hence, the patient's medication history should be reviewed.

Assessment of cognitive complaints should determine the onset, severity, duration, and domains of cognitive changes. Effective screening tools for cancer-associated cognitive impairment are lacking. Brief screening tools such as the Mini-Mental State Examination lack adequate sensitivity to detect a subtle decline in cognitive performance. A comprehensive neuropsychological evaluation is helpful to identify the specific cognitive domains of deficit. Patient-reported outcome tools (e.g., the Functional Assessment of Cancer Therapy-Cognitive Function and the Cognitive Failures Questionnaire) can also be used to assess how cognitive impairment affects health-related quality of life.

Nonpharmacologic Interventions

For nonpharmacologic interventions, cognitive training has been evaluated for its role in managing chemotherapy-associated cognitive impairment. Cognitive training is a type of brain training, aiming to improve neurocognitive function. Studies have suggested that the benefits of cognitive training result from an overall enhancement in self-reported quality of life.

The NCCN survivorship panel has also made practical suggestions that can be included in self-management and coping strategies, including the use of planners, reminder notes, and smartphone technology (NCCN 2015b).

Pharmacologic Interventions

Quality data on pharmacologic interventions of cancer-associated cognitive impairment are currently lacking (Chan

2015). This could be because of the poor understanding of biological mechanisms behind this phenomenon. Data are conflicting on the evaluation of short- and medium-term cognitive measures between psychostimulants such as methylphenidate and modafinil and controls.

One randomized, double-blind, crossover trial that enrolled childhood cancer survivors of acute lymphoblastic leukemia or brain tumors found that methylphenidate was more effective than placebo in improving attention, cognitive flexibility, and processing speed (Conklin 2007). However, these results were inconsistent with those of another trial of patients with breast cancer (Mar Fan 2008). Modafinil was studied in another trial involving two phases (Kohli 2009). In the first phase, all patients received modafinil 100 mg once daily for 3 days, followed by 200 mg once daily during a 4-week open-label period. In the subsequent phase, patients achieving a positive response in attention and memory in the first phase were randomized to an additional 4 weeks of modafinil 200 mg/day or placebo. In the assessment of short- and medium-term cognitive measures between modafinil and controls, no statistically significant difference in cognitive measures was observed.

Gingko biloba was studied for preventing cognitive impairment in patients with breast cancer receiving adjuvant chemotherapy. Patients were randomized to receive gingko biloba 60 mg twice daily or placebo. The intervention commenced at the second cycle of chemotherapy and continued until 1 month after the end of chemotherapy. There were no significant differences in either subjective or objective cognitive measures between the two groups (Barton 2013).

CANCER-RELATED FATIGUE

Cancer-related fatigue (CRF) refers to a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness related to the disease or anticancer treatments that is not proportional to recent activity and that interferes with usual functioning.

Clinical Presentation and Risk Factors

Often experienced by patients with cancer, CRF can interfere with daily functioning. Patients rate fatigue as more distressing than other cancer- or treatment-induced symptoms, including nausea and pain. Fatigue can affect patients with cancer both cognitively and emotionally. Cancer-related fatigue can also negatively affect the quality of life of patients with cancer; individuals who report significant levels of fatigue decrease their participation in activities that make their lives meaningful. These patients also describe higher levels of emotional distress than individuals who do not have fatigue (Berger 2012).

The trajectory of CRF among individuals receiving treatment for early-stage breast cancer was evaluated in an observational study. In that study, CRF was assessed at the start of treatment, at the end of treatment, and at 2-month intervals after treatment. Breast cancer survivors, compared with healthy controls, reported longer-lasting fatigue in the week before all four study assessments ($p<0.05$). These differences appeared to be clinically meaningful. A greater percentage of patients than healthy controls scored in the abnormal range on this measure during each assessment ($p<0.05$). Patients receiving radiotherapy alone had their most severe fatigue at the end of treatment, and patients who received multimodality treatment (chemotherapy and radiation) had their most severe fatigue up to 2 months after chemotherapy (Jacobsen 2007).

Prevalence

Occurrence of fatigue is highly prevalent among cancer survivors. However, the underlying mechanisms of CRF and the factors that contribute to CRF are unclear. Many factors related to the cancer and/or its treatment, such as abnormalities in energy metabolism, hormonal changes, chronic stress responses, anxiety, depressive disorders, anemia, and altered sleep patterns, may lead to CRF. Cancer-related fatigue may also occur because of cancer-related symptoms such as pain, nausea, and dyspnea. Alterations in the hypothalamic-pituitary-adrenal axis, alterations in the cellular immune system, and reactivation of latent herpes virus may also contribute to fatigue. In addition, research suggests that inactivity leading to impairment in the cardiorespiratory fitness and muscle function of patients with cancer can worsen and/or perpetuate CRF. Recent studies have also suggested that chemotherapy leads to dysregulation of proinflammatory cytokine concentrations (Eyob 2016).

Current Management

Quality data pertaining to the prevention and treatment of CRF are lacking. Nonpharmacologic management, which includes exercise, cognitive behavior therapy (CBT), and patient education, is currently recommended. Pharmacologic therapies have limited roles because experimental studies are lacking, and a significant placebo response has occurred in randomized trials. A poor understanding of CRF's biological mechanisms also contributes to the limited therapeutic options.

Screening and Assessment

The ASCO guidelines on screening, assessment, and management of fatigue in adult cancer survivors recommend that all health care providers routinely screen for the presence of CRF from the point of diagnosis onward, including after the end of primary treatment (Bower 2014). Screening should be done and documented using a quantitative or semiquantitative assessment. For example, on a 0–10 numeric rating scale (0 = no fatigue; 10 = worst fatigue imaginable), mild fatigue is indicated by a score of 1–3, moderate fatigue by 4–6, and severe fatigue by 7–10. For laboratory evaluation, a CBC, comprehensive metabolic panel, and endocrine evaluation such as thyroid-stimulating hormone concentrations should be

done, depending on the presence of symptoms and the onset and severity of CRF.

Nonpharmacologic Interventions

The ASCO guidelines show that it is important to address all the factors that may contribute to CRF, including nutritional deficits, pain, emotional distress such as depression and anxiety, sleep disorders, anemia, and comorbidities. Exercise is highly recommended for the management of CRF. Recommendations for physical activity are described under Lifestyle-Related Prevention.

Several other nonpharmacologic therapies such as CBT and psychoeducational therapies may also reduce fatigue in cancer survivors. Survivors should be referred to psychosocial service providers who specialize in cancer and are trained to deliver empirically based interventions. In addition, interventions such as mindfulness-based approaches, yoga, qigong, and acupuncture may have benefits for the treatment of CRF. However, more studies are required before standardized recommendations can be made for these therapies.

Pharmacologic Interventions

Pharmacologic interventions for the management of CRF are currently limited. Although some evidence suggests that psychostimulants and wakefulness agents (e.g., methylphenidate and modafinil) can be used effectively to treat CRF in patients with advanced disease or those on active treatment, there is no evidence of their effectiveness in reducing fatigue in patients who are disease free after active treatment, other than those who are treated for obstructive sleep apnea. In addition, small pilot studies have evaluated the impact of supplements such as ginseng and vitamin D on CRF. However, evidence of their effectiveness is inconsistent.

SLEEP DISORDERS

Cancer survivors commonly have sleep disorders. Sleep disorders are generally classified as insomnia, sleep disturbances, and/or excessive sleepiness. Insomnia has been identified as one of the most prevalent sleep disorders among cancer survivors. Sleep disorders may lead to many negative health outcomes, including poor health-related quality of life, fatigue, poor healing, cognitive dysfunction, lost work productivity, accidents, poor relationships, and increased health care costs.

Prevalence, Clinical Presentation, and Risk Factors

Sleep disorders affect 30%–50% of all patients with cancer and cancer survivors and often coexist with other symptoms such as pain, fatigue, anxiety, and depression (NCCN 2015b). Cancer survivors can have difficulty falling asleep and/or maintaining sleep. Insomnia can be problematic because it may decrease daytime functioning and lead to poor quality of life and increased distress. It is also suggested that insomnia can be exacerbated among survivors by chronic adverse effects of anticancer treatment, emotional distress, medications, and maladaptive behaviors, including changes in sleep patterns and poor sleep hygiene (e.g., an excessive amount of naps and sleep caused by CRF).

Current Management

Screening and Assessment

Information on a patient's sleep pattern and quality is usually obtained through interviews. Insomnia is generally defined in patients as difficulty falling asleep and/or maintaining sleep at least three times per week within 4 weeks (NCCN 2015b). Chronic insomnia is defined as ongoing insomnia symptoms over at least 3 months. For management of insomnia, it is important to assess whether patients have any treatable contributing factors, including comorbidities such as hypothyroidism, caffeine intake late in the day, emotional distress, shift work, and other symptoms such as fatigue and pain that may contribute to insomnia.

Nonpharmacologic Interventions

Physical activity is well established within the literature to improve sleep among cancer survivors. One randomized controlled trial compared a standardized yoga intervention combined with standard of care with standard of care alone to improve moderate to severe sleep disruption among cancer survivors. Participants in the yoga group had greater improvements in global and subjective sleep quality, daytime functioning, and sleep efficiency and reductions in hypnotic use. A Cochrane review also suggested that exercise can improve sleep at a 12-week follow-up (Mishra 2012). However, the best standardized exercise/activity regimen to improve insomnia in cancer survivors is unknown. Exercise is recommended in the morning and/or afternoon for cancer survivors who are pursuing exercise activities, to avoid any interference with sleep.

Cognitive behavioral therapy may also benefit cancer survivors for the management of insomnia. In a randomized, placebo-controlled study, survivors receiving CBT had significant and lasting improvements in insomnia and sleep quality. However, adding armodafinil did not result in improved sleep quality or increased CBT efficacy (Roscoe 2015).

Other nonpharmacologic strategies such as sleep hygiene education are also deemed important. For example, it is recommended that survivors reduce bright light (computer or phone screens or light sources close to the eyes) within a few hours before bedtime and during the night. In addition, they should avoid alcohol, caffeine, nicotine, and heavy meals close to bedtime. Survivors should also be limited to one short nap per day if they have fatigue and should be encouraged to make the sleep environment comfortable, including keeping the room dark and quiet (NCCN 2015b).

Pharmacologic Interventions

For survivors who have insomnia, hypnotics may be useful for temporary relief. Several agents, including zolpidem, zaleplon, eszopiclone, ramelteon, temazepam, and suvorexant, may assist with sleep initiation. However, few studies have specifically investigated these agents for improving sleep quality in cancer survivors. In addition, these agents may be associated with dependence, abuse, and withdrawal; thus, survivors taking these agents should be reassessed every 1–3 months to determine whether the treatments are still needed.

The NCCN survivorship guideline does not recommend routine use of antidepressants, antihistamines, atypical antipsychotics, other benzodiazepine receptor agonists, and supplements (e.g., melatonin) for the treatment of insomnia because of the limited effectiveness data available. Furthermore, these agents are associated with significant risks; hence, they should be used with caution.

One study suggested that mirtazapine can increase nighttime sleep in patients with cancer (Cankurtaran 2008). Survivors with depression and anxiety may benefit from mirtazapine. Literature also suggests using melatonin for the management of insomnia in cancer survivors. A small, randomized, double-blind, placebo-controlled study suggested that treatment with melatonin for 4 months can improve sleep quality (Chen 2014).

SEXUAL HEALTH

Concerns regarding sexual dysfunction during survivorship are common, but they are poorly addressed and managed among cancer survivors. Pharmacologic therapies (chemotherapy and/or hormonal therapies) and treatment directed toward the pelvis (surgery and/or radiation) may impair sexual function. Depression and anxiety, which are common psychosocial problems encountered by cancer survivors, may further exacerbate the severity of sexual dysfunction.

Erectile Dysfunction Among Male Survivors

In men, anticancer treatment modalities have the potential to damage blood vessels, which may lead to reduced blood circulation to the penis as well as damage to the autonomic nervous system. Thus, male cancer survivors are at risk of developing erectile dysfunction (ED). A high prevalence of ED occurred among males treated for prostate cancer and colorectal cancer. Currently, guidelines specific to the management of ED in cancer survivors are not available, but the American Urological Association has developed guidelines for the management of ED that can be used for male cancer survivors (NCCN 2015b; AUA 2005). Individuals who are concerned about their sexual function should undergo a comprehensive evaluation, including screening for potential psychosocial distress (anxiety and depression), substance abuse (drug or alcohol use), and drug therapies (e.g., hormone therapy or opioids) that may contribute to a higher risk of ED. Management of ED should begin with modifying risk factors such as smoking cessation, using weight loss, increasing physical activity, and avoiding excess alcohol consumption. Use of oral phosphodiesterase type 5 (PDE5) inhibitors (e.g., sildenafil, vardenafil, and tadalafil) improves ED in patients with cancer as well as cancer survivors. An adequate trial of PDE5 inhibitors is defined as at least five separate occasions at the maximum dose before reporting the trial as noneffective (NCCN 2015b). A different PDE5 inhibitor can be tested after the failure of first-line PDE5 inhibitor therapy, or when a patient cannot tolerate a certain PDE5 inhibitor. Referral to an urologist for evaluation of other therapies should be considered if the second trial of PDE5 inhibitors fails.

Specific Issues Among Female Survivors

Female cancer survivors may have many types of sexual dysfunction after cancer treatment. Cervical cancer survivors often receive radiation and have poor sexual functioning, including reduced arousal, lubrication, orgasm, and satisfaction, and increased pain compared with those who were treated with surgery alone. Breast cancer survivors can have chemotherapy-induced amenorrhea, which may lead to sexual dysfunction.

Chemotherapy agents such as cyclophosphamide and taxanes can induce amenorrhea by disrupting follicular maturation or damaging primordial follicles, which leads to a large reduction in circulating estradiol concentrations. Thus, the management of female sexual dysfunction in cancer survivors should first address the underlying problems, which include physiological (menopause) and psychological distress–related (anxiety and depression) issues.

Vaginal dryness and pain are common complaints among female cancer survivors. Some studies suggest that pelvic floor muscle training can reduce sexual pain and improve arousal, lubrication, orgasm, and satisfaction. In addition, several types of pharmacologic agents including water-, oil-, or silicone-based lubricants; vaginal moisturizers; and topical lidocaine may help alleviate vaginal symptoms. Local administration of estrogen (e.g., pills, rings, or creams) has been used in postmenopausal women without cancer. Safety data, however, are limited for using vaginal estrogen in cancer survivors. Recently, a randomized controlled, double-blind trial evaluated the role of aqueous 4% lidocaine in estrogen-deficient breast cancer survivors with severe penetrative dyspareunia (Goetsch 2015). In this study, aqueous 4% lidocaine was applied to the vulvar vestibule for 3 minutes before vaginal penetration. Results suggest that breast cancer survivors can have comfortable sexual intercourse after applying lidocaine to desensitize the vulvar vestibule before sexual penetration.

Ospemifene is a selective estrogen receptor modulator that is currently approved for the management of postmenopausal-related vulvar and vaginal atrophy. Clinical trials show that ospemifene reduces vaginal dryness and dyspareunia. However, no data suggest using ospemifene in cancer survivors.

The NCCN survivorship guidelines suggest that the drug can be considered in cancer survivors, but only among those who do not have hormone-sensitive cancers (NCCN 2015b).

Flibanserin is a multifunctional serotonin agonist and antagonist that improves sexual functioning in premenopausal women with hypoactive sexual desire disorder. Although flibanserin is not approved in the cancer survivor population, clinical trials show that it improves the number of satisfying sexual events and sexual desire as measured by the Female Sexual Function Index. However, flibanserin is associated with an increased risk of dizziness, somnolence, nausea, and fatigue. Currently, patients eligible for flibanserin must be enrolled in a Risk Evaluation and Mitigation Strategies program to receive the drug because of its increased risk of hypotension and syncope.

Infertility

Infertility is a potential health problem among cancer survivors because many cancer survivors are of childbearing age. Before cancer treatment, the risks of infertility post-cancer treatment should be discussed with patients, and health care providers should evaluate whether fertility preservation could be an option for these patients.

In women, one common consequence of treatment for breast cancer is hormonal depletion, which may result in premature menopause. Among patients receiving doxorubicin and cyclophosphamide followed by docetaxel, the incidence of amenorrhea was 54.7% at 24 months in those younger than 40, 89.1% in those 40–50 years of age, and 96.8% among those older than 50 (Swain 2009). In addition, tamoxifen use increases the rates of amenorrhea more drastically.

The ASCO clinical practice guidelines provide information regarding fertility preservation for patients with cancer (Loren 2013). Several strategies, including embryo or oocyte cryopreservation and conservative gynecologic surgery, can preserve fertility in females. Men should be advised of a potentially higher risk of genetic damage to sperm collected after chemotherapy. Thus, sperm cryopreservation should be done before treatment. Fertility discussions should be individualized.

In addition to cytotoxic chemotherapy, recipients of targeted therapies such as bevacizumab may have an increased risk of ovarian failure. The manufacturer of bevacizumab states that providers should inform women who are of reproductive potential about the risk of ovarian failure before beginning bevacizumab treatment. In addition, survivors receiving tyrosine kinase inhibitors (imatinib, dasatinib, and nilotinib), thalidomide, and lenalidomide should be aware that these agents are teratogenic in animal models and/or humans. In one report, women who conceived while using imatinib had reported abnormalities and complex malformations, which are clearly of concern. Current recommendations do not favor continuing tyrosine kinase inhibitor therapy during pregnancy.

PREVENTIVE HEALTH

About one-third of all cancers are caused by modifiable lifestyle factors, which include tobacco use, diet, alcohol, and obesity. Unfortunately, despite knowing the harms of poor lifestyle factors, many cancer survivors continue with these behaviors after treatment. Many also forgo recommended cancer screenings for secondary malignant neoplasms and follow-up surveillance. This section will focus on several lifestyle-related changes that are important for cancer survivors. These include exercise, weight and nutrition management, and smoking cessation. Immunizations and prevention of infections are also important and are addressed in a different chapter.

Secondary Malignant Neoplasms

Because the overall cancer rate is higher among survivors than among the general population, it is crucial that survivorship care incorporate screening and early detection for secondary primary cancers. In the United States, about 18% of all malignancies are a second (or subsequent) cancer (Howlader 2016). Having several risk factors may contribute to the onset of second cancers, including genetic susceptibilities, shared causative factors (e.g., smoking, alcohol, obesity, and environmental exposures), aging, and mutagenic effects of cancer treatment (e.g., radiotherapy and chemotherapy).

The American Cancer Society has provided specific recommendations for adult survivors of several cancers, which are summarized in Box 1-1. For survivors of childhood, adolescent, and young adult cancer, the Children's Oncology Group has provided extensive recommendations in its long-term follow-up guidelines (COG 2013).

Lifestyle-Related Prevention

Exercise

Obesity and low levels of physical activity are associated with higher risks of cancer recurrence and mortality. Studies have also suggested that weight gain after cancer diagnosis is associated with a higher risk of recurrence. Healthy lifestyle habits such as engaging in routine physical activity and maintaining a healthy diet and weight improve health outcomes and quality of life. Incorporating exercise and physical activity may also reduce other comorbidities such as CV events.

Survivors should routinely be assessed for their readiness to participate in physical activity and the level of physical activity in which they engage. Common barriers to physical activities include having inadequate time to exercise, lacking access to an exercise environment, having a lack of safety knowledge for exercise, having a lack of knowledge of appropriate exercise activities, and having physical limitations that result from symptoms.

Currently, both the American Cancer Society and the American College of Sports Medicine (ACSM) have made physical activity recommendations for cancer survivors

Box 1-1. Screening and Early Detection Recommendations for Adult Cancer Survivors

Breast cancer history
- Provide age- and sex-appropriate screening for patients with an average risk
- Provide an annual gynecologic assessment for postmenopausal women receiving selective estrogen receptor modulator therapies

Prostate cancer history
- Provide age-appropriate screening in men with an average risk
- Survivors having undergone radiation therapy may have a slightly higher risk of bladder and colorectal cancers and may need to follow screening guidelines for higher-risk individuals, if available
- Survivors presenting with hematuria should receive a thorough evaluation to rule out bladder cancer, including urologist referral for cystoscopy
- Survivors presenting with persistent rectal bleeding, pain, or other symptoms of unknown origin should be referred to the gastroenterologist and the treating radiation oncologist for a thorough evaluation for rectal cancer

Colorectal cancer history
- Provide age-appropriate screening for patients with an average risk, except for female colorectal cancer survivors with Lynch syndrome
- Female colorectal cancer survivors with Lynch syndrome should receive annual endometrial sampling and transvaginal ultrasonography

Head and neck cancer history
- Provide age-appropriate screening for patients with an average risk
- Screen survivors for lung cancer with low-dose CT for high-risk patients, depending on smoking history
- Screen head and neck survivors for another head and neck cancer and esophageal cancer because these survivors are at increased risk

Information from: Cohen EEW, LaMonte SJ, Erb NL, et al. American Cancer Society head and neck cancer survivorship care guidelines. CA Cancer J Clin 2016;66:203-39; El-Shami K, Oeffinger KC, Erb NL, et al. American Cancer Society colorectal cancer survivorship care guidelines. CA Cancer J Clin 2015;65:428-55; Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol 2016;66:43-73; and Skolarus TA, Wolf AM, Erb NL, et al. American Cancer Society prostate cancer survivorship guidelines. CA Cancer J Clin 2014;64:225-49.

(Rock 2012; Schmitz 2010). All survivors should be encouraged to avoid inactivity or a sedentary lifestyle and return to daily activity as soon as possible. All survivors are recommended to engage in a moderate level of physical activity after cancer treatment (e.g., 150 minutes of moderate aerobic exercise such as fast walking, cycling, or swimming per week with an additional two or three sessions per week of strength training such as weight-lifting), unless contraindicated. Activities should be tailored to each person's ability and preferences. In addition, walking programs are generally safe for most cancer survivors. The ACSM recommends that cancer survivors begin this type of program after consulting with their physicians, but without any formal exercise testing (e.g., a stress test) (Schmitz 2010). Survivors who are at a higher risk of injury (e.g., those living with neuropathy and cardiomyopathy) should be referred to a physical therapist or exercise specialist for a risk evaluation. Breast cancer survivors with lymphedema should also consider meeting with an exercise specialist before initiating upper-body strength training exercise.

Weight and Nutrition Management

Weight management is essential among cancer survivors. Around 62% of breast cancer survivors are overweight (BMI greater than 25 kg/m^2), of whom 30% are classified as having obesity (BMI greater than 30 mg/m^2). Obesity is a risk factor for postoperative complications, secondary cancer, cancer recurrence, and development of diabetes. Women who were underweight (BMI less than 18.5 kg/m^2) within 12 months after diagnosis, however, had a statistically significant 53% increased risk of breast cancer–specific mortality.

Strategies for weight management should be discussed to prevent weight gain for normal and overweight survivors/survivors with obesity. Clinicians should discuss portion control and refer overweight survivors/survivors with obesity to dietitians for weight management. Strategies for weight loss such as medications or bariatric surgery are not well studied among cancer survivors. Survivors whose BMI is in the underweight range, however, should be engaged in discussions about nutrition, and current guidelines advise underweight survivors to increase their frequency of eating and to avoid fluid intake with meals, which may help with weight gain. In addition, smoking status, dental health, swallowing and taste/smell disorders, and GI motility should be assessed.

Survivors should be encouraged to make informed choices about food to ensure variety and an adequate nutrient intake. Current recommendations suggest that survivors maintain a dietary pattern that is high in vegetables, fruits, and whole grains and legumes; low in saturated fats; and limited in alcohol consumption. Fish and poultry are also recommended,

whereas red and processed meats should be limited. Although the current literature does not provide consensus on soy consumption, the NCCN guidelines on survivorship suggest a moderate daily consumption of soy foods (three or fewer servings per day) (NCCN 2015b).

Pharmacologic agents (e.g., corticosteroids and progestins) are generally used in patients with advanced cancer to improve cancer-related cachexia; however, no evidence exists for their routine use in cancer survivors. Supplements (e.g., vitamins and minerals) are not routinely recommended in most survivors unless they have documented deficiencies (e.g., in survivors of gastric cancer) or comorbidities that require supplementation.

Smoking Cessation

Despite all the known health risks associated with smoking, an American Cancer Society survey found that about 10% of all cancer survivors are smokers, with smoking prevalence highest among survivors of bladder, lung, and ovarian cancers (Westmaas 2014). In addition, according to the National Health and Nutrition Examination Survey, 64% of all cancer survivors who regularly smoked before their cancer diagnosis continue to smoke (Tseng 2012). Several characteristics, such as being female, of young age, and Hispanic, were identified for continued smoking after cancer treatment. Studies have also identified barriers that impede patients with cancer and cancer survivors from smoking cessation. These factors include stress, dependence, environmental factors, lack of resources, lack of support for quitting, and life challenges that result from their cancer diagnosis.

The NCCN has developed a guideline to provide guidance specifically on smoking cessation in patients with cancer (NCCN 2015a). In patients who are current smokers, providers should assess whether patients are ready to quit within the next 30 days. In those who are ready to quit, providers should assess nicotine dependency according to the amount of cigarettes smoked per day, how soon the patient smokes after waking up in the morning, and whether the patient requires other forms of tobacco. Other information includes why patients' previous attempts to quit smoking have failed and patients' previous experience with smoking cessation aids. This is important information to personalize an appropriate smoking cessation plan for the patient. For patients who are not ready to quit, providers are encouraged to engage them in a motivational dialogue about smoking and to ensure that they are aware of the disease-specific risks of smoking and the benefits of quitting.

After assessment, providers should establish a personalized quit plan for each patient. A quit day should be set, preferably within 2 weeks or at least 2 or more weeks before any planned surgical procedures. Because smokers with cancer often have high-level nicotine dependence, the guidelines recommend a multimodal approach to cessation therapy, which involves three tenets: behavior therapy through counseling, pharmacotherapy, and close follow-up with retreatment as needed. Current data analyses recommend a combination of frontline approaches that include a combination nicotine replacement therapy (NRT) or varenicline together with behavior therapy for smoking cessation for patients with cancer to enhance the success rate (Cahill 2013). Combination NRT typically includes the combination of a nicotine patch with a short-acting NRT, which could be a lozenge, gum, inhaler, or nasal spray. The safety of combination NRT has been shown, and it outweighs the potential risks. Recent reviews suggest that evidence is insufficient that NRT increases the risk of myocardial infarction or CVD (Mills 2014; Stead 2012). In addition, data are conflicting to suggest that NRT can lead to cancer or that it promotes chemoresistance. However, in a large cohort study of 3320 individuals, NRT use was not a significant predictor of lung cancer, whereas smoking was identified as a lung cancer predictor (Murray 2009).

To determine response, smoking status should be assessed at 12 weeks and at the end of pharmacotherapy if the therapy is longer than 12 weeks. In patients who relapse, second- and third-line therapies are recommended. Second-line therapies include varenicline with combination NRT or bupropion in combination with NRT. As third line, recommendations include combination therapy with varenicline, bupropion, and NRT. Other single-agent third-line options include clonidine and nortriptyline (Table 1-3).

OVERALL APPROACH

Transition from active treatment to after-treatment care is critical to the long-term health of cancer survivors. Unfortunately, the model of posttreatment care to achieve the best outcome still has many unknown factors. Many studies have evaluated the barriers that may affect delivery of optimal survivorship care (Tejeda 2013; Lewis 2009; Hewitt 2007). Barriers are generally classified as physician related or patient related. Physician-related barriers include lack of a physician's time and inadequate knowledge to manage survivorship issues. Patient-related barriers include lack of awareness, reluctance to discuss sensitive psychosocial issues, and poor adherence to the recommended treatment. Both barrier categories lead to poor management of health issues among cancer survivors.

Standards for Survivorship Care

A major clinical barrier to standardizing survivorship care is the lack of guidance on the treatment of survivors with diverse cancer types who are treated across different age spectrums with different approaches and modalities that continue to evolve over time. Hence, in the past decade, efforts were concentrated on ensuring quality survivorship care could be delivered to survivors by identifying the key elements. In the 2005 Institute of Medicine report "From Cancer Patient to Cancer Survivor: Lost in Transition," four components of survivorship care are embraced: prevention and detection of new cancers and recurrent cancer, surveillance for recurrence or new

Table 1-3. Agents Used for Smoking Cessation

Agent	Standard Dose	Duration (wk)	Warnings
Varenicline	• Initiate dosing 1–2 wk before quitting; initiate at 0.5 mg orally once daily on days 1–3, followed by 0.5 mg orally twice daily on days 4–7 and 1 mg orally twice daily in weeks 2–12 (if tolerated)	12	Monitor for risks of increased hostility, depression, or suicidal behavior
Bupropion	• Initiate dosing 1–2 wk before quitting; initiate at 150 mg orally once daily on days 1–3, followed by 150 mg orally twice daily starting on day 4, if tolerated	7–12	Monitor for risks of increased hostility, depression, or suicidal behavior; contraindicated in patients with seizure risks (brain metastases or stroke), those with concurrent use of monoamine oxidase inhibitors or tamoxifen, and those with closed-angle glaucoma
Combination nicotine replacement therapy	• 21-mg patch + short-acting nicotine replacement therapy • If 21-mg patch is not effective, consider increasing patch dose to 35 or 42 mg, as clinically indicated	12	Generally well tolerated, and nicotine toxicity is rare and transient
Clonidine	• Oral: Initiate 0.1 mg twice daily, and titrate 0.1 mg/day every 7 days as needed; dose range 0.15–0.45 mg/day • Transdermal: Initiate 0.1-mg/24-hour patch once every 7 days and increase by 0.1 mg at 1-wk intervals as needed; dose range 0.1–0.3 mg/day	3–10	Should be initiated 48–72 hours before the quit day; treatment should not exceed 3–4 wk after smoking cessation. Dose tapering overall days at the end of therapy is recommended, particularly in hypertensive patients
Nortriptyline	• Initiate 25 mg/day and titrate the dose to 75–100 mg/day 10–28 days before quit day	≥ 12	Monitor for anticholinergic adverse effects; may not be appropriate in the older adult population

primary cancers, interventions for long-term and late effects from cancer and its therapies, and coordination between specialists and primary care providers to ensure that all of the survivor's needs are met. To further expand the essential elements that are crucial for survivorship care, the Livestrong Foundation has created a list of essential elements that are crucial for survivorship care (Table 1-4).

The Institute of Medicine has also suggested that all health care providers should use systematically developed evidence-based clinical practice guidelines, assessment tools, and screening instruments to identify and manage the late effects of cancer and its treatment. Many guidelines have been published to address the standards of survivorship programs over the past few years. To ensure the quality of these survivorship care programs, ASCO has published and endorsed two guidelines on the treatment of breast and prostate cancer survivors. The NCCN has published a general guideline that addresses different aspects of survivorship. The Children's Oncology Group has also published a long-term follow-up guideline on the survivorship of patients with childhood, adolescent, and young adult cancers.

Survivorship Care Plans

To ensure a successful transition to posttreatment care, the literature advocates using a survivorship care plan. These care plans include cancer treatment summary and follow-up plans for survivors to keep as health care records and share with their primary care providers. They are designed to ensure that appropriate post-cancer treatment services are provided to the survivors. Furthermore, these plans define the responsibilities of cancer-related, non–cancer-related, and psychosocial providers.

Role of a Pharmacist

There are tremendous opportunities for pharmacists to cotreat cancer survivors with other health care professionals. Pharmacists are in the best position to resolve drug-related problems in cancer survivors. Apart from medications to treat complications of cancer treatment, cancer survivors often receive maintenance therapies (e.g., hormonal therapies and targeted therapies), many of which are susceptible to drug-drug interactions and adverse drug reactions

Table 1-4. Essential Elements of Survivorship Care Defined by Livestrong Foundation

Tier	Essential Elements
Tier 1 – All medical settings must provide direct access or referral to these elements of care	• Survivorship care plan, psychosocial care plan, and treatment summary • Screening for new cancers and surveillance for recurrence • Care coordination strategy that addresses care coordination with primary care physicians and primary oncologists • Health promotion education • Symptom management and palliative care
Tier 2 – All medical settings should provide direct access or referral to these elements of care for high-need patients and to all patients, when possible	• Late effects education • Psychosocial assessment • Comprehensive medical assessment • Nutrition services, physical activity services, and weight management • Transition visit and cancer-specific transition visit • Psychosocial care • Rehabilitation for late effects • Family and caregiver support • Patient navigation • Educational information about survivorship and program offerings
Tier 3 – All medical settings should strive to provide direct access or referral to these elements of care	• Self-advocacy skills training • Counseling for practical issues • Ongoing quality improvement activities • Referral to specialty care • Continuing medical education

Information from: Livestrong Foundation. The Essential Elements of Survivorship Care. [homepage on the Internet].

(Table 1-5). Ambulatory care pharmacists can carry out medication reconciliation to identify and reduce polypharmacy- and drug-related problems. Pharmacists can also play an important role in assessing survivors' adherence to prescribed maintenance therapies.

One longitudinal, observational study depicted the medication changes that took place from diagnosis of breast cancer until 1 year after the last dose of anticancer treatments. Medication changes that occurred during the survivorship phase reflected the introduction of adjuvant hormonal therapies and medications to manage the long-term psychosocial effects of cancer and its treatment (Loh 2016). Several medications were also introduced during survivorship, such as bisphosphonates and calcium/vitamin D supplements (for preventing osteoporosis and treatment of musculoskeletal symptoms) and antidepressants (for the treatment of depression). An increased medication burden for the treatment of chronic diseases (e.g., CV medications) also occurred during the survivorship phase.

Many cancer survivors are also interested in using herbal medications and/or supplements to manage posttreatment complications, and pharmacists can play a role in providing cancer survivors with information on the appropriate use of such supplements and screening for potential drug interactions.

In addition to medication management, pharmacists can use screening tools to monitor patients' well-being and to recommend evidence-based therapies to manage cancer- or treatment-related symptoms. Moreover, as survivors remain in remission with their cancers and continue to age, these survivors may also have chronic illnesses that require long-term follow-up and monitoring. Pharmacists can work together with cancer survivors to adjust their chronic medications and achieve their treatment goals. Pharmacists can also provide counseling to reduce lifestyle risk factors, such as smoking cessation and nutrition management.

Recently, a randomized controlled trial evaluated the effectiveness of a standardized transitional program for the treatment of breast cancer survivors (Chan 2016). In this study, a multidisciplinary care team (including a pharmacist) conducted psychoeducation workshops for breast cancer survivors who had just completed chemotherapy. The pharmacist's role was to discuss toxicity management and medication use with breast cancer survivors. Results showed that such interventions reduce physical symptoms and CRF in breast cancer survivors. This evidence suggests that pharmacists can play a significant role in the treatment of cancer survivors within a multidisciplinary care team.

Table 1-5. Clinically Important Drug-Drug Interactions with Maintenance Anticancer Agents During Survivorship

Maintenance Anticancer Agents	Survivors Using These Agents	Drugs Susceptible to Interactions	Clinical Consequences
Tamoxifen, raloxifene	Breast cancer	Selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (e.g., fluoxetine, duloxetine, paroxetine)	Decreased activation of tamoxifen and raloxifene, leading to reduced efficacy
		Warfarin	Increased anticoagulant effect
Imatinib	Chronic myelogenous leukemia, GI stromal tumor	St. John's wort	Decreased concentrations of imatinib, potential for reduced anticancer effect
		Warfarin	Increased risk of bleeding
Dasatinib	Chronic myelogenous leukemia, GI stromal tumor	Proton pump inhibitors, histamine-2 blockers	Decreased absorption of dasatinib
		Verapamil	Increased dasatinib exposure, increased risk of toxicities (e.g., thrombocytopenia and QT prolongation)
Methotrexate	Acute lymphoblastic leukemia	NSAIDs, sulfamethoxazole/trimethoprim	Reduced methotrexate clearance, potential for increased toxic effects
Mercaptopurine	Acute lymphoblastic leukemia	Allopurinol	Increased mercaptopurine concentrations, increased risk of toxicities (myelosuppression and hepatotoxicities)

Practice Points

Survivorship care plans are helpful to coordinate the care required for cancer survivors who are transitioning care back to their general practitioner. These components should be included in a survivorship care plan:

- **Account for survivors' risk of chronic illnesses, such as diabetes and CVD, and outline methods to address these risks.**
- **Assess and address psychosocial needs.**
- **Include information about fertility planning for survivors of reproductive age.**
- **Include known adverse effects (persistent or late onset) of cancer and cancer treatment.**
- **Include screening guidelines and symptoms of cancer recurrence, including second primary cancers.**
- **Discuss and incorporate survivors' values and preferences regarding their care.**
- **Use discussions about cancer-related concerns as teachable moments to educate survivors about lifestyle behavioral changes.**

CONCLUSION

As cancer cure rates improve, focus is increasing on improving patients' survivorship. Cancer survivors are required to make many adjustments to their lifestyle, even though there are still a lot of unknowns regarding the optimal survivorship care delivery. Some examples include a lack of extensive evidence on the most appropriate strategies to manage toxicities. Moreover, the most appropriate time to transition a cancer survivor from specialized cancer centers to the community is unknown. Many community providers are unfamiliar with survivorship health risks and are uncomfortable in treating survivors with complex health issues. Currently, the ideal mode for implementing survivorship care plans is still unknown. Despite these challenges, survivorship as part of the cancer continuum is widely acknowledged, and continuous efforts are required to improve the science of cancer survivorship.

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Self-Assessment Questions

1. A 45-year-old woman is being followed up in your heart failure (HF) clinic. She was previously treated for mediastinal diffuse large B-cell lymphoma with anthracycline-based chemotherapy, and her cancer is currently in remission. She reports intermittent symptoms of shortness of breath and increased exercise intolerance at times, and she was given a diagnosis of stage C HF. Her current drugs include metoprolol extended release (XL) 200 mg daily, atorvastatin 40 mg daily, and furosemide 40 mg twice daily. Her kidney and liver functions are normal; her blood pressure is 145/75 mm Hg, and her heart rate is 71 beats/minute. Which one of the following would best manage this patient's HF symptoms?

   A. Initiate digoxin 0.125 mg orally once daily.
   B. Initiate enalapril 20 mg twice daily.
   C. Discontinue metoprolol XL, and initiate losartan 100 mg daily.
   D. Increase furosemide dose to 80 mg orally twice daily.

Questions 2–4 pertain to the following case.

T.A. is a 39-year-old woman who was treated for stage 2B breast cancer 1 year ago. She had a full mastectomy and completed four cycles of chemotherapy with docetaxel and cyclophosphamide. She is currently receiving adjuvant tamoxifen for 5 years. On her routine visit, T.A. has complaints of numbness and neuropathic pain in her fingers and toes, which prevents her from preparing meals. Otherwise, she sleeps well and has no other symptoms. Her medical history includes diabetes and hyperlipidemia.

2. Which one of the following would best assess the severity of T.A.'s sensory neuropathy symptoms?

   A. Patient Neurotoxicity Questionnaire
   B. Nerve Conduction Test
   C. NCI-CTCAE version 4.03
   D. Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity

3. Which one of the following is best to recommend for pain management for T.A.?

   A. Oxycodone
   B. Duloxetine
   C. Lamotrigine
   D. Amitriptyline

4. T.A. is counseled on the benefits of exercise. Given her medical history, which one of the following is best to recommend for T.A.?

   A. Swim 60 minutes every week.
   B. Meet with an exercise specialist before exercising.
   C. Receive one session of strength training every week.
   D. Wait 2 years before beginning an exercise program.

5. Which one of the following best describes the role of cognitive training in the treatment of post-chemotherapy cognitive impairment in patients?

   A. Reduces the proinflammatory cytokines.
   B. Best used in combination with pharmacologic therapy.
   C. Improves cognitive function and enhances self-reported quality of life.
   D. Evidence lacking to establish role.

6. In a study that evaluated the role of bevacizumab in colorectal cancer in 179 women, 95 received bevacizumab in combination with chemotherapy, and 84 received chemotherapy alone. At the end of the study, ovarian failure had developed in 32 women in the combination group and 2 women in the chemotherapy-only group. Which one of the following best describes the number needed to harm on the development of ovarian failure because of bevacizumab?

   A. 3
   B. 18
   C. 33
   D. 43

7. A 72-year-old man previously received external beam radiation therapy for localized prostate cancer. He currently receives leuprolide depot every 3 months for maintenance therapy. The patient reports that he has lost interest in exercising since his cancer diagnosis. He also reports a loss of appetite, sleeping a lot, and a feeling of worthlessness, and he is unable to concentrate during the day. Furthermore, he was recently unable to sustain an erection during sexual intercourse. Which one of the following is best to recommend for this patient?

   A. Discontinue leuprolide depot.
   B. Add sildenafil.
   C. Add bupropion.
   D. Add fluoxetine.

8. Your multidisciplinary team evaluates the accessibility of the health services provided to cancer survivors at your cancer center. Which one of the following care services is most important to make available to all cancer survivors?

   A. Nutrition support
   B. Family and caregiver support
   C. Rehabilitation for late effects of cancer
   D. Screening for second primary neoplasms

Questions 9 and 10 pertain to the following case.

R.S. is a 52-year-old woman who is a postmenopausal breast cancer survivor. R.S. has received tamoxifen for 3 years.

9. Which one of the following is the best surveillance strategy for R.S.?

   A. CT scan of her lower pelvis annually
   B. Mammogram every 2 years
   C. Transvaginal ultrasonography annually
   D. Annual gynecology assessment

10. R.S. has complaints of vaginal dryness and pain during sexual intercourse. Which one of the following is best to recommend for R.S.?

   A. Ospemifene
   B. Estrogen tablets
   C. Aqueous 4% lidocaine
   D. Vaginal ring estrogen

11. Which one of the following cancer survivors is at highest risk of poor mental health?

   A. A 19-year-old childhood leukemia survivor who could not complete school because of treatment
   B. A 58-year-old breast cancer survivor with strong family support
   B. A 62-year-old prostate cancer survivor who was healthy before his cancer diagnosis
   C. A 60-year-old lymphoma survivor who had received a hematopoietic stem cell transplant

12. A retrospective cohort study tracks the cardiovascular disease (CVD) profiles in survivors of adolescent and young adult cancers. A total of 24,839 cancer survivors and 239,073 healthy controls are recruited. A total of 119 cancer survivors and 432 healthy controls develop CVD. Compared with the healthy controls, which one of the following ratios best describes the likelihood of cancer survivors having CVD?

   A. 1.81
   B. 2.65
   C. 3.63
   D. 4.79

Questions 13 and 14 pertain to the following case.

J.W. is a 28-year-old survivor of early-stage Hodgkin lymphoma. Three months ago, he was treated with two cycles of chemotherapy with radiation, and his disease is currently in remission. On follow-up today at the survivorship clinic, J.W. has complaints that he is constantly tired, but he has difficulty maintaining sleep. He has no other signs or symptoms.

13. Which one of the following is best to recommend for J.W. to manage his tiredness?

   A. Initiate modafinil 100 mg once daily.
   B. Initiate ginseng extract.
   C. Initiate methylphenidate.
   D. Increase physical activity.

14. Which one of the following would best improve J.W.'s sleep quality?

   A. Lorazepam
   B. Eszopiclone
   C. Mirtazapine
   D. Zaleplon

Questions 15–17 pertain to the following case.

S.R. is a 56-year-old survivor of laryngeal cancer. He received concurrent cisplatin and radiation as primary treatment, and his cancer is currently in remission. His comorbidities include hypertension and hyperlipidemia. S.R. has a 35 pack-year smoking history and he has been placed on combination nicotine replacement therapy (NRT) with behavior therapy over the past 4 months. On follow-up today at the survivorship clinic, S.R. reports that he has started smoking again a few days ago.

15. Which one of the following is best to recommend to assist S.R. in smoking cessation?

   A. Behavioral therapy
   B. Bupropion
   C. Varenicline with combination NRT
   D. Combination NRT with behavior therapy

16. S.R. has lost a significant amount of weight during treatment. However, his BMI of 17 kg/m^2 has remained unchanged since remission. Which one of the following is best to recommend for S.R. at this time?

   A. Change him to an all-organic diet.
   B. Initiate megestrol acetate 800 mg once daily.
   C. Initiate prednisone 60 mg once daily.
   D. Assess his swallowing ability.

17. Which one of the following cancers is it best to recommend S.R. be screened for?

   A. Esophageal
   B. Colorectal
   C. Prostate
   D. Thyroid

18. A 46-year-old survivor of chronic myelogenous leukemia is receiving maintenance dasatinib. He has gastritis and requires a medication for symptomatic relief. Which one of the following is best to recommend for this patient?

   A. Give omeprazole 40 mg once daily.
   B. Give esomeprazole 20 mg twice daily.
   C. Give Gaviscon 15 mL every 6 hours as needed.
   D. Give famotidine 20 mg twice daily.

19. A 35-year-old woman has completed four cycles of doxorubicin and cyclophosphamide for the treatment of early-stage breast cancer. Before chemotherapy, her baseline ejection fraction is 54%. She has no other cardiac risk factors and is currently asymptomatic. Which one of the following is best to recommend regarding cardiac ejection fraction reassessment in this patient?

    A. Reassessment of cardiac ejection fraction is not required.
    B. Reassess within 6 months of the last doxorubicin dose.
    C. Reassess within 12 months of the last doxorubicin dose.
    D. Reassess within 18 months of the last doxorubicin dose.

20. A 62-year-old survivor of multiple myeloma has received four cycles of bortezomib, thalidomide, and dexamethasone as induction treatment. In her survivorship care plan, which one of the following toxicities is best to recommend for close monitoring over the next 12 months?

    A. Vaginal dryness
    B. Peripheral neuropathy
    C. Cardiotoxicity
    D. Cancer-related fatigue

Learner Chapter Evaluation: Cancer Survivorship.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Compose an appropriate management plan for a cancer survivor with treatment-induced cardiotoxicity.
13. Evaluate the pharmacologic and nonpharmacologic options for managing peripheral and central neurotoxicities.
14. Develop a treatment plan to manage cancer-related fatigue and sleep disorders in cancer survivors.
15. Compose recommendations associated with sexual health and infertility in cancer survivors.
16. Apply screening and lifestyle recommendations to individualize care in cancer survivors.
17. Justify the importance of implementing a survivorship care plan.
18. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Vaccination in the Patient with Immunocompromise

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LEARNING OBJECTIVES

1. Distinguish between innate, adaptive, cellular, and humoral immunity, including the role of and the cells involved in each.
2. Assess the impact of diseases and therapies on immunity.
3. Develop a risk-benefit tool to determine the vaccination plan for a particular patient.
4. Using current data and the available vaccines, justify the optimal vaccination product and timing for the patient with immunocompromise.
5. Evaluate opportunities to improve vaccination rates and emerging trends in vaccinations in the patient with immunocompromise.

ABBREVIATIONS IN THIS CHAPTER

ALL	Acute lymphoblastic leukemia
GVHD	Graft-vs.-host disease
HBV	Hepatitis B virus
HSCT	Hematopoietic stem cell transplantation
Hib	*Haemophilus influenzae* type b
HPV	Human papillomavirus
IDSA	Infectious Diseases Society of America
IIV	Inactivated influenza vaccine
IPV	Inactivated polio vaccine
LAIV	Live-attenuated influenza vaccine
MCV	Meningococcal conjugate vaccine
MMR	Measles, mumps, and rubella (vaccine)
MPSV	Meningococcal polysaccharide vaccine
PCV	Pneumococcal conjugate vaccine
PPSV	Pneumococcal polysaccharide vaccine
SOT	Solid organ transplantation

Table of other common abbreviation.

BACKGROUND AND DEFINITIONS

Vaccinations are the cornerstone in preventing many avoidable infectious diseases and maintaining public health. However, data on the safety and efficacy of vaccines are limited, particularly in patients with immunocompromise, because these patients were excluded in most original vaccine studies; however, this population remains at increased risk of severe infections when immunity against vaccine-preventable disease is lost or reduced, thereby increasing the risk and severity of these infections. Revaccinations should be considered, but the exact timing and schedules of vaccinations are often unclear.

This chapter focuses on the different types of vaccine-preventable diseases, available vaccine products, data regarding the use of each vaccine in individuals with immunocompromise, and recommendations for administration. The prototypical example of immunocompromise is a patient with cancer who has received a hematopoietic stem cell transplant (HSCT). The greatest focus is on recommendations in this extremely immunosuppressed population. Other immunocompromised conditions that warrant considerations for revaccination, including solid organ transplantation (SOT) and HIV infection, are discussed briefly. As a member of the health care team, pharmacists can play a vital role by identifying patients at risk of loss or lack of immunity and selecting the appropriate vaccination products and schedules to best protect these patients from vaccine-preventable diseases and their complications.

Immunity Types

To understand how vaccinations work, a fundamental working knowledge of the general principles of immunity is necessary. The immune

system consists of two main subsystems–the innate immune system and the adaptive immune system–which work together to provide effective immune responses. The innate system provides a nonspecific response to pathogens and includes anatomic barriers (skin, mucous membranes), physiologic barriers (fever, gastric acid), inflammatory and complement pathways, and the initial mononuclear and granulocytic response to pathogens. In contrast, the adaptive immune system is composed of B cells and T cells. B cells are primarily responsible for the humoral response to antigens, whereas T cells are responsible for cell-mediated immunity. In humoral immunity, B cells are produced in the bone marrow and they mature in the lymph nodes. Within these lymph nodes, naive B cells are exposed to antigens, undergo somatic hypermutation at the Fab region, and mature into plasma cells. These plasma cells then produce antibodies specific to that particular antigen. T cell–mediated immunity works primarily against intracellular pathogens. T cells mature in the thymus and then travel to the bloodstream as two subtypes: CD4 (T helper) and CD8 (T cytotoxic) cells. CD4 cells recognize major histocompatibility complex II (MHC II) proteins, which are found on all immune cells. CD8 cells recognize MHC class I proteins, which act as markers of body cells and are found on all nucleated cells. Unlike B cells, which can recognize antigens in their native form, T cells can only recognize antigens that have been processed and presented by antigen-presenting cells.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of vaccine-preventable diseases
- Standard vaccination recommendations for the general public
- Formulations of available vaccines
- The importance of vaccinations and the impact of lack of vaccinations on public health

Table of common laboratory reference values.

ADDITIONAL READINGS

The following resources have additional background information on this topic:

- IDSA. 2013 Infectious Diseases Society of America Clinical Practice Guideline for Vaccination of the Immunocompromised Host
- Tomblyn M, Chiller T, Einsele H, et al. American Society for Blood and Marrow Transplantation. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143-238.

IMMUNIZATION BASICS

Mechanism of Action of Vaccinations

Protection against viral diseases may be achieved through passive or active immunity. Passive immunity occurs when preformed antibodies are transferred to an unimmunized individual. Examples of passive immunization include the transfer of maternal antibodies through the placenta to the fetus and intravenous immunoglobulin administration. Passive transfers confer temporary immunity against particular illnesses, but as the antibodies are destroyed, the patient eventually loses immunity. Conversely, active immunization involves the exposure of an unimmunized individual to a pathogenic agent. On exposure, the immune system begins to process the antigen and mounts both humoral and cellular responses to the specific antigen. Active immunity can develop because of active infection or use of immunizations. Ideally, active immunizations should activate the innate immune system as well as both arms of the adaptive immune system.

Types of Vaccines

Live attenuated vaccines contain laboratory-weakened versions of the original antigen. These vaccines incite a strong cellular and antibody response and usually produce long-term immunity with only one or two doses. Because these vaccines contain live organisms, there is a slight possibility that the organism could revert to a more virulent form and produce active disease in patients with immunocompromise. Currently available live attenuated vaccines include influenza (LAIV), measles/mumps/rubella (MMR), varicella (Varivax), and zoster (Zostavax).

Inactivated vaccines are prepared by destroying a pathogen with chemicals, heat, or radiation. Although this method removes the risk of pathogen-induced disease, it results in weaker immune response and necessitates additional booster shots to maintain immunity. Currently available inactivated vaccines include the inactivated influenza (IIV) and the inactivated polio (IPV) vaccines.

Subunit vaccines consist of only the epitopes that most easily stimulate the immune system. An example of a subunit vaccine is the hepatitis B virus (HBV) vaccine.

Conjugate vaccines are a special type of subunit vaccine. In a conjugate vaccine, antigens or toxoids from an organism are linked to polysaccharides from the outer coating of the microbe to stimulate immunity. Conjugate vaccines currently used include the *Haemophilus influenzae* type b (Hib), pneumococcal (PCV), and meningococcal (MCV) vaccines.

Polysaccharide vaccines consist purely of the cell wall polysaccharide from bacteria. These vaccines stimulate B cells without the assistance of helper T cells; thus, in patients with immunocompromise, polysaccharide vaccines are not uniformly immunogenic because B cells are not yet developed or mature. Examples include the pneumococcal polysaccharide vaccine (PPSV) and the meningococcal polysaccharide vaccine (MPSV).

Toxoid vaccines are created by inactivating bacterial toxins with formalin. Instead of mounting a response against the bacteria, these vaccines stimulate an immune response against bacterial toxins. Current examples of toxoid vaccines include diphtheria and tetanus.

SCOPE OF THE ISSUE

The term *immunocompromised* can describe many individuals with different diseases or undergoing various therapies. Populations with the best-described vaccine-related recommendations include HSCT recipients, patients undergoing treatment for cancer, individuals with HIV infection, SOT recipients, patients with primary immunodeficiency, and patients with asplenia.

To better characterize the impact of disease or therapy on immunity, the Infectious Diseases Society of America (IDSA) has published definitions for patients with high- and low-level immunosuppression (Box 2-1). The distinction between high and low immunosuppression levels is important because those with high-level immunosuppression are at a greater risk of infectious complications. In addition, disease states such as HIV can vary in severity, resulting in different recommendations depending on an individual's level of immunosuppression.

Box 2-1. IDSA Categorization of Degree of Immunosuppression According to Disease and Therapy

High Level:

- Primary immunodeficiency disorder (e.g., severe combined immunodeficiency [SCID])
- Receiving cancer chemotherapy
- Within 2 mo after solid organ transplantation
- HIV infection with a CD4 T-lymphocyte count < 200 cells/mm^2 for adults and adolescents and < 15% for infants and children
- Receiving daily corticosteroid therapy with a dose > 20 mg (or > 2 mg/kg/day for patients < 10 kg) of prednisone or equivalent for at least 14 days
- Receiving certain biologic immune modulators, specifically TNF-α blockers or rituximab
- Stem cell transplantation, depending on type of transplant, type of donor, stem cell source, and posttransplant complications such as graft-vs.-host disease

Low Level:

- Asymptomatic patients with HIV infection with a CD4 T-lymphocyte count of 200–499 cells/mm^3 for adults and adolescents and percentage of 15%–24% for infants and children
- Lower daily doses of systemic corticosteroids than for high-level immunosuppression for > 14 days or "every-other-day" corticosteroid therapy

Those receiving methotrexate < 0.4 mg/kg/week, azathioprine < 3 mg/kg/day, or mercaptopurine < 1.5 mg/kg/day

TNF = tumor necrosis factor.
Information from: Tomblyn M, Chiller T, Einsele H, et al. American Society for Blood and Marrow Transplantation. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143–238.

DATA AND RECOMMENDATIONS

Vaccinations in HSCT Recipients

Certain diseases, specifically those that affect cells of immune system such as leukemia, lymphomas, and some sarcomas, can cause immune function compromise up-front when untreated. Furthermore, treatments for cancer can induce a wide range of immunosuppression and dysfunction.

Pediatric patients are most likely to receive cancer diagnoses and be initiated on chemotherapy when they are receiving routinely scheduled childhood vaccines. As a result, their vaccination schedule may be interrupted, leading to decreased levels of protection against vaccine-preventable diseases. The youngest pediatric oncology patients are at an even higher risk because chemotherapy can affect both B-cell and plasma cell development in the bone marrow, leading to profound and lasting immunodeficiency (Nilsson 2002). In the adult oncology population, data regarding immunity pre- and posttreatment are often lacking. One of the biggest hurdles is with quantifying the effect of immunizations because most studies use surrogate end points such as occurrence of disease or antibody titer. Disease occurrence is a difficult end point to use because many vaccine-preventable diseases have a low occurrence rate at baseline. Using antibody titers solely to gauge response is also challenging because most vaccines do not have specific thresholds for antibody titers that define immunity. Finally, there is wide heterogeneity with respect to immunocompetence because factors such as tumor type and therapy type/duration/response can affect an individual's level and extent of immunosuppression.

Traditional chemotherapy agents, particularly alkylating agents and purine nucleoside analogs, disrupt immunity. The agent most commonly implicated in therapy-associated immunosuppression is cyclophosphamide, particularly when given as a single agent at high doses (Fauci 1971). Purine analogs, including fludarabine and mercaptopurine, can induce significant lymphocyte depletion by affecting active and resting lymphocytes (Mackall 2000). Over the past decade, targeted therapies and immunotherapy agents such as rituximab, alemtuzumab, and antithymocyte globulin have become commonplace in cancer treatment. These agents target specific parts of the immune system (rituximab targets CD20 on the surface of B cells, alemtuzumab targets CD52 on the surface of T cells, and antithymocyte globulin targets all T cells), resulting in severe consequences. Alemtuzumab can cause complete T-lymphocyte depletion for up to 12 months after receipt of therapy (Hill-Cawthorne 2012).

Several studies have evaluated the effect of chemotherapy on the persistence of antibody titers against certain vaccine-preventable diseases, particularly HBV, MMR, tetanus, polio, influenza, and pneumococcal disease (Lehrnbecher 2009; Yu 2007; Zignol 2004). In one of the more robust evaluations, researchers studied 192 pediatric patients who completed first-line therapy for malignancy and attained remission after treatment. About 70% of the patients were given a diagnosis of hematologic malignancies. Before therapy, vaccination and exposure history were obtained. When possible, antibody titers were obtained to assess immunity to HBV, MMR, tetanus, and polio. After completing chemotherapy, antibody titers were collected to detect a lack (if pretreatment titers were unavailable) or loss (if pretreatment titers showed immunity) of immunity. Results showed that 7%–52% of patients had either lack or loss of immunity after cancer treatment (Zignol 2004).

In HSCT, myeloablative chemotherapy induces a period of profound pancytopenia, which can last from days to weeks. The recovery of cells starts with neutrophil, monocyte, and natural killer cell recovery, followed by platelet and red cell recovery. The last cells to recover are typically the B and T lymphocytes. Recovery of the immune system can take several months and, in some patients, several years. At the same time, some chemotherapy regimens damage mucous membranes, disrupting parts of the innate immune system and providing a source for infectious seeding.

Antibody titers to vaccine-preventable diseases decline during the 1–10 years after an allogeneic or autologous HSCT (Ljungman 1989). For a vaccine to mount a clinically meaningful response, adaptive immunity must be at least partly reconstituted. B-cell recovery usually begins at least 3 months after HSCT. In patients treated with rituximab posttransplantation, this recovery can be delayed an additional 6 months.

Evidence for individual vaccinations in HSCT recipients is limited, with some vaccinations clearly having more robust data than others (Tomblyn 2009).

Influenza

Influenza can be severe and life threatening in HSCT recipients, largely because of secondary bacterial infections such as pneumonia. The increased risk of influenza infection remains for several years after HSCT, particularly in patients with chronic graft-vs.-host disease (GVHD). The mortality from influenza is also significantly higher in the HSCT population than in the immunocompetent population, with a mortality rate of almost 15% (Ljungman 2001). Given this, lifelong seasonal influenza vaccination with the inactivated product is recommended for all HSCT candidates and recipients (Rubin 2014; Tomblyn 2009). The timing of vaccination should be considered to maximize response. In a trial evaluating one versus two doses of the influenza vaccine in 48 autologous and allogeneic HSCT recipients, all patients lacked a response to the immunization when given within 6 months of HSCT; however, 25% responded when the immunization was given between 6 months and 2 years, and 60% responded when the vaccine was administered after 2 years posttransplantation. Administering a second dose of vaccination did not significantly improve response rates (Engelhard 1993).

Formulation of the influenza vaccine used should also be considered, especially in the immunocompromised population. The inactivated injectable influenza vaccine is available as either trivalent or quadrivalent, and both formulations are recommended for use in HSCT recipients older than 6 months. Data are limited regarding use of the high-dose inactivated formulation posttransplantation; therefore, it is currently not recommended. Use of the inactivated intradermal vaccine in this HSCT population is also limited; one study including 26 HSCT recipients had efficacy with this formulation, but given the data limitations, intradermal influenza is not recommended in HSCT recipients (Gelinck 2009). Finally, use of the live-attenuated influenza intranasal vaccine (LAIV) is contraindicated in patients with immunocompromise. Although transmission of active disease has not been seen, the risks of disease transmission outweigh the potential benefits of LAIV.

Given the available data, the inactivated formulation of seasonal influenza vaccination at the standard dose is recommended for all adult and pediatric HSCT recipients older than 6 months. Vaccinations should start 6 months after HSCT, with consideration for starting 2 months earlier if an influenza community outbreak occurs. For patients within 4 months of transplantation, vaccination is unlikely to be fully effective.

Streptococcus pneumoniae

In the HSCT population, a loss of antibody concentrations against *S. pneumoniae* has been shown in several studies. Invasive pneumococcal infections (pneumonia, sepsis, meningitis) can be life threatening, particularly given the functional hyposplenism that can be caused by the use of total body irradiation or the occurrence of chronic GVHD. Incidence is higher in patients with chronic GVHD and in those receiving allogeneic HSCT. Infections can occur as soon as 3 months posttransplantation, but the median time of occurrence of pneumococcal disease is generally 9–15 months posttransplantation. Vaccination against *S. pneumoniae* is crucial and can significantly affect the maintenance of health posttransplantation.

Response to the PCV formulation is generally higher than response to the polysaccharide formulation, although the conjugate vaccine has a narrower spectrum of coverage. In an evaluation of conjugate versus polysaccharide vaccine, there were no responders to the polysaccharide vaccine at 6 months posttransplantation compared with a 39% response rate to the conjugate vaccine. At 12 months after transplantation, the PPSV23 vaccine resulted in immunity

in 56% compared with 91% in those receiving PCV (Kumar 2007). Most of the post-HSCT immunization studies with pneumococcal vaccines used the PCV7 vaccine. These data have largely been extrapolated to PCV13, which replaced PCV7 in 2010.

The time to initiate pneumococcal vaccination remains unclear. One trial compared response to the three-dose conjugate vaccine series starting at either 3 months or 9 months posttransplantation. Response rates were similar between groups, leading the authors to conclude that early vaccination may be preferred because it can protect against early and late pneumococcal disease. However, if vaccinations are initiated early, antibody titers can fall to below protective levels within a year. Therefore, it may be advisable to follow antibody titers and administer booster doses as needed (Cordonnier 2008). Current IDSA guidelines recommend that all adult and pediatric posttransplant recipients be vaccinated with the pneumococcal vaccine. At least three doses of PCV13 should be given, beginning 3–6 months after transplantation. Doses should be separated by 4–8 weeks, with a fourth dose of vaccination given at 12 months posttransplantation. In patients with chronic GVHD, the fourth dose should be a conjugate vaccine dose (because of poor response to the polysaccharide vaccine). In patients without chronic GVHD, the PPSV23 vaccine can be administered as the fourth dose because it expands coverage over more strains of pneumococcal infection.

Tetanus/Diphtheria/Pertussis

Immunity to both tetanus and diphtheria is lost during and after HSCT, but patients are at no higher risk of contracting infections than the normal population. Pertussis, however, can be a cause of significant morbidity posttransplantation. *Bordetella pertussis* is highly contagious and spreads through respiratory droplets. In addition, HSCT recipients with preexisting pulmonary complications may be even more vulnerable to complications from pertussis. Given this risk, vaccination for all HSCT recipients is highly recommended. Two standard-dose levels of acellular pertussis are available in combination vaccines. The "reduced" dose is represented by a "p" (diphtheria and pertussis vaccine [Tdap]), and the "full" dose is represented by a "P" (diphtheria, tetanus, and pertussis vaccine [DTaP]).

Three studies evaluated the efficacy of pertussis vaccination in adolescents and adults posttransplantation using the "reduced-dose" formulations. All three trials had a very poor response to the reduced-dose acellular pertussis (Papadopoulos 2010; Small 2009; Papadopoulos 2008). Therefore, consensus guidelines recommend use of the full-dose pertussis to maximize the likelihood of a response. Beginning 6 months after transplantation, patients should receive three doses of DTaP with at least 1 month between each dose. A booster dose, using Tdap, can be administered at least 12 months after the first DTaP dose to maximize immunologic response. Table 2-1 provides vaccine recommendations regulating to HSCT.

Hepatitis B

In the HSCT population, a lack of donor antibody or presence of GVHD can further increase the risk of infection. In the transplant setting, donor and recipient serostatus can also affect the decision to vaccinate. Risk of hepatitis is lowest when both recipient and donor are hepatitis B surface antigen (HBsAg) negative, whereas highest risk is when the recipient is seronegative and the donor is positive. In the latter case, the recommendation is to vaccinate the recipient before transplantation to reduce the risk of severe primary HBV infection. It is often not feasible to administer three doses of the vaccine in the recommended 6-month time interval. For all transplant patients, the full three-dose series should be administered beginning a minimum of 6 months after transplantation. After completing the three-dose series, antibody titers should be measured, and if the patient does not have a reproducible titer, a second three-dose series should be considered (Rubin 2014).

Measles/Mumps/Rubella

Measles infection in patients with immunocompromise can be severe and may have atypical presentations with prolonged viral shedding periods. There have been reports of fatal cases of measles in HSCT recipients because most lose measles immunity after transplantation. Adults who have had natural measles infection before transplantation, however, usually retain immunity for years after transplantation. Given that the measles vaccine (as part of the MMR vaccine) is a live attenuated vaccine, it cannot be administered immediately posttransplantation. Administration of the MMR vaccine should only be considered at least 2 years after transplantation in allogeneic HSCT recipients without GVHD or ongoing immunosuppression.

Varicella Zoster

Herpes zoster reactivation commonly occurs after HSCT because of decreased immunity. The risk of reactivation is about 30%–50% 6 months posttransplantation, with GVHD in allogeneic transplantation a significant risk factor. Herpes zoster infections in HSCT recipients can result in secondary bacterial infections and postherpetic neuralgia. The infection can also more easily disseminate and result in pneumonia, sepsis, encephalitis, and death. Most centers use antiviral prophylaxis posttransplantation to help reduce the risk of infection. Use of the varicella vaccine is controversial in HSCT recipients. If vaccination is deemed necessary, only the varicella vaccine, not the zoster vaccine, should be used because the varicella vaccine is less potent and can be safer posttransplantation, whereas the safety of the zoster vaccine has not been well established. If administered, the vaccine should not be given until a minimum of 2 years posttransplantation to reduce the risk of viral activation.

Table 2-1. Vaccine Recommendations Before or After HSCT

Vaccine[a]	How Long After HSCT to Initiate (mo)	No. of Doses	Additional Information
H. influenzae type b conjugate (Hib)	3	3	
Hepatitis A	6	2	
Hepatitis B (HBV)	6	3	
Human papillomavirus (HPV)	6	3	
DTaP, DT, Td, Tdap	6	3	Age < 7: DTaP x 3 doses Age ≥ 7: DTaP x 3 doses, OR one dose Tdap, then two doses DT or Td
Influenza, inactivated vaccine (IIV)	4	1	Administer annually
Meningococcal conjugate vaccine (MCV4)	6	2	Recommended for age 11–18 and high-risk populations
Measles, mumps, and rubella (MMR)	24	2	Patients should not have GVHD or be taking immunosuppressive medications
Pneumococcal conjugate vaccine (PCV13)	3	3	
Pneumococcal polysaccharide vaccine (PPSV23)	12	1	Patient should not have GVHD
Polio, inactivated vaccine	3	3	
Varicella live vaccine	24	2	Consider administration if varicella seronegative, > 24 mo post-HSCT, no GVHD, and no immunosuppression

[a]All other live vaccines, unless listed in the table, are contraindicated for use in the posttransplant period.

GVHD = graft-vs.-host disease; HSCT = hematopoietic stem cell transplantation.

Adapted with permission from: Rubin LG, Levin MJ, Lungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44-100.

Neisseria meningitidis

Similar to other diseases, immunity to meningococcal disease is reduced posttransplantation. Similar to pneumococcal vaccination, meningococcal vaccinations are available in the conjugate (MCV4) and polysaccharide (MPSV4) form. The MCV4 is more immunogenic and likely more effective than the polysaccharide vaccine in HSCT recipients. For meningococcal disease, vaccination is only required for patients who are at risk, including those age 2 months to 10 years, those with functional or anatomic asplenia, those with complement deficiency, military recruits, and college students. A two-dose vaccination series should be administered 2 months apart, beginning at least 6 months after transplantation, followed by a booster every 5 years for patients who remain at risk.

Polio

Immunity to polio is progressively lost after HSCT. Acute GVHD can accelerate the loss of antibody titers. All adult and pediatric HSCT recipients should be vaccinated with the IPV beginning 6–12 months after transplantation. Patients should receive three doses total. The live oral polio vaccine is contraindicated in patients with immunocompromise and their contacts because of the risk of active infection and potential paralysis.

Human Papillomavirus

Genital human papillomavirus (HPV) infection is a late complication of allogeneic HSCT and can occur in up to one-third of long-term survivors. Associations between immunosuppression and HPV are lacking in the HSCT population; nonetheless, patients who are qualified to receive HPV vaccination should receive it starting 6–12 months after transplantation, for three doses total.

Vaccinations in Patients with Cancer

Patients receiving therapy for cancer may have varying degrees of immunosuppression as a result. With the

intensification of cancer treatments and the increased use of immunosuppressive monoclonal antibodies, the risk of vaccine-preventable diseases is further increased. Data regarding vaccinations in patients with cancer are from trials conducted before the advent of antibody-based therapy, so these results may not accurately reflect the risks and benefits of vaccinations in patients receiving more modern therapies. Table 2-2 summarizes current recommendations for vaccinations in patients with cancer.

Influenza

There is good evidence to support the administration of the seasonal influenza vaccination in patients with cancer. Since the early 1970s, over 20 published studies have evaluated the effectiveness of influenza vaccination in a variety of oncology populations (Pollyea 2010). In patients with solid tumors, influenza vaccination resulted in higher survival rates, likely because of the ability to maintain treatment intensity and schedule (Earle 2003). In patients with hematologic malignancies, response rates may be lower, depending on malignancy type and the time between flu season and administration of active chemotherapy. For patients with lymphoma, the receipt of rituximab almost uniformly predicts nonresponse to influenza vaccination for 6 months post-rituximab therapy (Rapezzi 2003). Although marginally effective, vaccine administration is safe for those with the highest level of immunosuppression during flu season. To maximize the likelihood of vaccination response, providers can consider administering influenza vaccination in between cycles of chemotherapy, but the most protection can be afforded to these high-risk oncology patients by appropriately vaccinating close contacts and health care workers (see section on vaccination of household contacts).

S. pneumoniae

Although patients with solid tumors respond appropriately to the pneumococcal vaccine, patients with hematologic malignancies have an impaired antibody response to PPSV23 once chemotherapy treatments are initiated. For patients with Hodgkin lymphoma or non-Hodgkin lymphoma requiring splenectomy, vaccination with PPSV23 both before and after splenectomy induces a reasonable antibody response. When pre- and post-splenectomy vaccination is not possible, administration of the conjugate vaccine series improves the response to a subsequent dose of polysaccharide vaccination in previously treated patients with Hodgkin lymphoma.

Table 2-2. Recommendations for Patients with Cancer

Vaccine	Recommendation	Timing of Administration
Hepatitis B (HBV)	Administer series in adults with lymphoid malignancies	≥ 3 mo post-chemotherapy or ≥ 6 mo post anti–B-cell antibody therapy
DTaP, Tdap	Administer single dose in adults with ALL or lymphoma	
Measles, mumps, and rubella (MMR)	Administer if due for standard recommendations	
Varicella/zoster	Administer if due for general population	
Influenza (live-attenuated, LAIV)	Contraindicated during chemotherapy	
Influenza inactivated (IIV)	Administer to all patients	Seasonal. In between cycles of chemotherapy
Pneumococcal vaccination (PCV13, PPSV23)	One or two doses of conjugate vaccine, followed by one dose of polysaccharide vaccine	Initial conjugate vaccination starts at diagnosis. Polysaccharide dose 8 wk after conjugate dose
H. influenzae type b (Hib) conjugate, hepatitis A, human papillomavirus (HPV), polio-inactivated (IPV)	Administer if patient not current with recommendations for dose of vaccine for immunocompetent individuals. Administration of inactivated vaccines other than influenza can be considered for children who are receiving maintenance chemotherapy, but doses administered while receiving induction or consolidation therapy should not be considered valid. Administration ≥ 2 wk before chemotherapy is preferred, if possible	

ALL = acute lymphoblastic leukemia.

Adapted with permission from: Rubin LG, Levin MJ, Lungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58:e44-100.

Box 2-2. PCV13 and PPSV23 Recommendations for Patients with Cancer or HIV Infection

PCV13:

- 2–5 yr: One dose of PCV13 if received three prior doses of PCV7/PCV13 before age 2, and two doses of PCV13 if received ≤ 2 doses of PCV7/ PCV13 before age 2
- 6–18 yr: Single dose of PCV13
- ≥ 19 yr: Single dose of PCV13. If received PPSV23 previously, administer PCV13 at least 1 yr after the last PPSV23 dose

PPSV23:

- HIV: ≥ 2 yr: Single dose of PPSV23 8 wk after completing PCV13; then a second dose 5 yr later

Current recommendations are to administer one or two doses of PCV13 to adults with newly diagnosed hematologic or solid malignancies and children with malignancies. The number of doses depends on age (Box 2-2).

Tetanus/Diphtheria/Pertussis

In patients with cancer, there are variable rates of loss of immunity to diphtheria, tetanus, and pertussis. In pediatric patients, baseline seronegativity rates after completing chemotherapy were highest for diphtheria, at 16.4%, compared with 3.9% and 3.5% for pertussis and tetanus immunity, respectively. Adult patients undergoing treatment of hematologic malignancies, particularly lymphoid malignancies, have the highest rates of seronegativity, especially to tetanus (Hammarstrøm 1998). Patients with acute lymphoblastic leukemia (ALL) or lymphoma should receive vaccination with either DTaP or Tdap starting at least 3 months after completing chemotherapy or after 6 months for those receiving anti–B-cell antibodies as part of their treatment.

Hepatitis B

In the patient with immunocompromise, hepatitis B infection is associated with serious consequences including liver failure and death. The risk of reactivation or infection in patients with cancer is highest for those with hematologic malignancies because of their greater need for blood transfusions and greater degree of immunosuppression (Lalazar 2007). In addition, certain chemotherapy agents increase the likelihood of viral reactivation of HBV. Hepatitis B virus DNA contains a glucocorticoid-responsive element that facilitates replication; hence, corticosteroid-containing treatments can potentially increase the risk of reactivation. For patients at high risk, use of a steroid-free chemotherapy regimen, if possible, can reduce the risk. Anthracycline chemotherapy has also been shown to stimulate HBV DNA in in vitro models (Hsu 2004; Tur-Kaspa 1986). The response rate to the HBV vaccine is poor in patients who are receiving active therapy for hematologic malignancies. Although supportive data are lacking, the IDSA guidelines state that it may be reasonable to vaccinate patients who were previously unvaccinated with the HBV vaccine either before or after discontinuing chemotherapy (Yagci 2007).

Varicella Zoster

Varicella zoster and herpes zoster infections pose serious and life-threatening risks to immunocompromised hosts. In a study of pediatric patients with ALL, 437 seronegative patients received two doses of varicella vaccine. Patients had to be in a complete remission for at least 1 year and have an absolute lymphocyte count of at least 700 cells/mm^3 and a platelet count of over 100,000/mm^3, and all maintenance therapy drugs had to be held 1 week before and after vaccination. Seroconversion occurred in 88% of patients after one dose and in 98% after two doses. Long-term follow-up of these patients showed 36 cases of varicella, 35 of which were mild and moderate, indicating attenuation achieved by administering the vaccine (Gershon 1984). There are case reports of adult patients developing disseminated zoster infections after administration of the zoster vaccine. Therefore, use of the zoster vaccine is contraindicated in patients actively receiving chemotherapy or immunosuppression. Consideration can be given to administering the vaccine at least 3 months after completing chemotherapy. There are no current data to recommend the use of an alternative vaccine, such as the varicella vaccine, in this patient population.

Vaccinations in Patients with HIV Infection

Individuals with HIV infection are at an increased risk of vaccine-preventable diseases and complications. Studies have shown that patients with HIV infection have infections such as *S. pneumoniae* and influenza at significantly higher rates than their noninfected counterparts. Hepatitis B rates are higher in patients with HIV infection because the virus has the same routes of transmission as HIV and is associated with increases in liver-related mortality. Human papillomavirus–related diseases are also higher in individuals with HIV infection than in noninfected patients, increasing HIV-positive women's risk of cervical cancer. Finally, patients with HIV infection are at risk of preventable diseases like tetanus, diphtheria, and pertussis. Compounding all of these risk factors is that HIV infection is associated with reductions in cellular immunity, which can lead to suboptimal responses to vaccinations. Overall, administering inactivated vaccines to children with HIV infection appears to be safe, with minimal adverse effects. Children with HIV infection have lower responses to vaccines than do immunocompetent individuals; however, a reduced response may provide adequate protection (Abzug 2006; Weinberg 2006).

Influenza

Data analyses have shown an association between increased mortality and HIV infection for influenza, with a high risk of acute cardiopulmonary events (Sheth 2011). A systematic review evaluated the efficacy and safety of influenza

vaccination in over 1500 patients with HIV infection across three randomized controlled trials and three observational trials. Vaccination was 85% effective in preventing influenza in adult patients. Patients with untreated HIV may have a diminished response to the inactivated influenza vaccination, but response rates improve in patients receiving appropriate combination antiretroviral therapy. Current IDSA guidelines recommend annual influenza vaccination for all patients, regardless of treatment status.

Pneumococcal Disease

Studies have shown that patients with HIV infection have a higher rate of *S. pneumoniae*–induced pneumonia and bacteremia-associated mortality than do individuals without HIV infection, regardless of antiretroviral therapy use (Grau 2005; Pesola 1992). A randomized trial compared 692 patients without HIV infection with 934 patients with HIV infection, of whom 59% received the 23-valent polysaccharide vaccine. Results showed that vaccination significantly reduced the risk of pneumonia in patients with HIV infection (Rodrigues-Barradas 2008). Administration of PCV is safe and effective in patients with HIV. Evaluations of children revealed that PCV7 is more immunogenic than PPSV23. One study evaluating the administration of two doses of PCV7 followed by a dose of PPSV23 reported response rates and durability of response similar to those in patients without HIV infection (Abzug 2006). Administration of PPSV has been studied primarily in the adolescent and adult populations with CD4 T-lymphocyte counts greater than 200 cells/mm^3. Although data are limited in patients with CD4 counts less than 200 cells/mm^3, the safety profile of the vaccine is favorable, so administration is recommended in these patients with consideration for revaccination after antiretroviral therapy results in CD4 counts greater than 200 cells/mm^3. Dosing recommendations are based on age and immunization history. See Box 2-2 for dosing recommendations.

H. influenzae Type b

Vaccination of children with HIV infection is unlikely to result in acceptable antibody titer concentrations against Hib, particularly in those not receiving combined antiretroviral therapy. Even those who do respond to vaccinations often have antibody responses that fall below the protective threshold within 1 year of vaccine administration. The standard vaccination schedule is still recommended in these patients. Children with HIV infection older than 59 months who have not received the Hib vaccine should receive one dose.

Varicella Zoster

Varicella vaccines appear to be safe and effective when used in children with HIV infection. A trial evaluated about 100 children up to 8 years of age with HIV who received the varicella vaccine. Investigators found no change in the children's CD4 T-cell percentage or viral load. Two doses administered 3 months apart resulted in good immune response. Long-term follow-up studies have shown that the vaccine is effective in preventing varicella and zoster more than 80% of the time. The best time to administer varicella vaccination in children and adult patients is 3 months after the start of combined antiretroviral therapy (Son 2010; Levin 2006). For adults with HIV infection, zoster vaccination is safe and immunogenic, but data are limited in patients younger than 50.

Diphtheria/Tetanus/Pertussis

Patients with HIV infection often have suboptimal concentrations of antibodies against pertussis, diphtheria, and tetanus after the standard vaccination series. Providers may administer booster vaccinations, which are effective in increasing antibody titers against pertussis and tetanus, though not to the same extent as in children without infection.

Hepatitis B

Hepatitis B is of particular concern in the population with HIV infection because it is commonly acquired in infants born to mothers with both HIV and HBV. Although the HBV vaccine is safe to administer to patients with HIV infection, responses can be highly variable (18%–72% of recipients attaining adequate concentrations of antibody protection) (Pasricha 2006). Two studies compared response rates with HBV vaccination in HIV-infected versus noninfected subjects. Both studies found that the rate of nonresponse to HBV vaccination was significantly higher in the HIV-positive subjects and that a large percentage of patients with HIV infection lacked protective concentrations of anti–hepatitis B surface antibody (HBs) titers, even after three doses of the standard vaccination. In patients not receiving combined antiretroviral therapy, only 30%–50% develop a protective antibody response compared with 60%–70% of patients receiving antiretroviral therapy (Sungkanuparph 2005; Keet 1992). To overcome a lack of response to vaccination, which is assessed after completing the three-dose series, providers may administer a single booster dose, repeat the entire three-dose series, or repeat the series with a double dose. Current recommendations state that adults and adolescents with HIV infection should receive the HBV vaccine series with consideration for high-dose HBV vaccine (40-mcg dose). One to 2 months after completing the vaccine series, patients should be tested for anti-HBs. If a concentration indicative of protection (greater than 10 mIU/mL) is not attained, a second three-dose series of HBV vaccine should be administered using either the standard or the high dose for children and the high dose for adolescents and adults.

Human Papillomavirus

The prevalence of HPV-related diseases is higher in the HIV-infected population than in the noninfected population, and HIV-positive women are at an increased risk of developing cervical cancer and cervical intraepithelial neoplasm.

A phase II open-label trial found that the three-dose HPV vaccine was effective in eliciting an immunologic response in 99 women age 16–23 with HIV infection, with the greatest response in those receiving active combined antiretroviral therapy. Human papillomavirus vaccination is strongly recommended for women 9–26 years old with HIV infection. The HPV4 vaccine is recommended over the bivalent HPV2 vaccine for additional prevention of genital warts.

MMR Vaccine

The MMR vaccine should be administered to children age 1–13 with HIV infection as well as to patients 14 years and older with HIV infection without measles immunity and with a CD4 count greater than 200 cells/mm^3. In children with HIV infection with poor CD4 T-lymphocyte counts (CD4 T-cell percentage less than 15 or T-cell lymphocyte count less than 200 cells/mm^3), the MMR vaccine should not be administered.

Vaccinations in SOT Recipients

Recipients of SOTs are treated for varying durations with immunosuppressive therapy. In addition, if organ rejection occurs, escalated immunosuppression may be warranted. These factors place recipients of SOT at a significant risk of infection.

Solid organ transplantation presents a unique opportunity because this immunocompromised state can be predicted and planned for in a way that other diseases or treatments cannot. Candidates for SOT may have to wait extended periods before a suitable donor is available. This provides an opportunity to boost antibody concentration against vaccine-preventable diseases, if appropriate. Therefore, vaccinations should be administered to SOT candidates before transplantation, preferably early in the disease process, when response to vaccinations is likely to be the greatest. In children with SOT, the standard vaccine series should be given with the goal of completing the primary series and any booster doses before transplantation (Danziger-Isakov 2013).

Posttransplantation, the optimal timing to resume immunizations has not been clearly identified. Many centers will wait a minimum of 2 months, but optimally 3–6 months after transplantation before administering immunizations, to maximize the immune response to vaccination. One exception is during community seasonal influenza outbreaks when vaccination is given earlier.

Influenza

Influenza can be severe in SOT recipients. Efficacy of influenza vaccination varies depending on many factors, including immunosuppressive regimen or recent rejection. In a trial of 51,730 adult renal transplant recipients, influenza vaccination in the first year posttransplantation was associated with lower risks of allograft loss and death (Hurst 2011). The Centers for Medicare & Medicaid Services recommends that SOT recipients receive influenza vaccinations before discharge from the hospital, when seasonally appropriate. Recipients of SOT who receive the IIV vaccine within 6 months of transplantation should be monitored closely and treated promptly if signs or symptoms occur. The LAIV is contraindicated in SOT recipients.

Pneumococcal Disease

Patients awaiting transplantation are at an increased risk of invasive pneumococcal disease. Recommendations for vaccination in SOT recipients vary between organizations. Studies have shown that in adults posttransplantation, conjugate vaccines produce immunologic responses similar to polysaccharide vaccines (Kumar 2003). Studies in which conjugate vaccine was administered before polysaccharide vaccine administration had similar titers and lack of additional benefit with the polysaccharide vaccine (Kumar 2008). Nonetheless, the CDC Advisory Committee on Immunization Practices recommends that SOT recipients receive both the conjugate and the polysaccharide vaccine as follows (CDC 2012):

- For patients who have not previously received either PCV13 or PPSV23, a single dose of PCV13 should be given, followed by a dose of PPSV23 at least 8 weeks later.
- For patients who have previously received one or more doses of PPSV23, a single dose of PCV13 should be given 1 year or more after the last PPSV23 dose was received.
- For patients who require additional doses of PPSV23, the first such dose should be given no sooner than 8 weeks after PCV13 and at least 5 years after the most recent dose of PPSV23.

At a minimum, children younger than 2 years should receive the conjugate PCV13 series, and patients older than 5 years should receive the polysaccharide PPSV23 vaccination.

Hepatitis B

Hepatitis B can be transmitted in SOT by HBsAg-positive or HBsAg-negative/anti–HBc (hepatitis B core antibody)-positive donors (Wachs 1995). The consequences of hepatitis infection can also be severe in the SOT population. In renal transplant recipients with chronic HBV infection, HBV-associated liver failure is a significant cause of mortality and graft loss (Breitenfeldt 2002). In kidney transplant candidates, HBV vaccination is less effective in patients on hemodialysis than in patients with earlier-stage renal disease. Liver transplant patients with cirrhosis often have a suboptimal response to therapy. In a study of 49 patients with cirrhosis, administration of the standard 20-mcg HBV vaccine monthly for three doses resulted in an appropriate antibody response in only 28% of patients, compared with 97% of healthy controls (Villeneuve 2000). Current guidelines recommend administering a high-dose vaccine (40 mcg), testing anti-HBs concentrations 1–2 months after the last dose

of the series as well as annually, and revaccinating if the anti-HBs concentrations fall below 10 mIU/mL (Mast 2006)

Varicella Zoster

Solid organ transplant recipients who are immunocompromised are at risk of severe varicella infections. In pediatric SOT recipients, varicella vaccination is recommended at least 4 weeks before transplantation. Patients with end-stage organ disease who have reduced seroconversion rates should receive two doses of the varicella vaccine, if feasible. Doses should be separated by 4 weeks for those 13 years and older and by 3 months for those 1–12 years. If the varicella vaccine cannot be administered before transplantation, posttransplant vaccination is not recommended because of the risk of disseminated varicella zoster infection. The exception would be in non-varicella immune pediatric renal or liver transplant recipients who are receiving minimal or no immunosuppression and who have had no recent allograft rejection.

Vaccinations for Household and Health Care Contacts of Individuals with Immunocompromise

One of the best ways to minimize the risk of vaccine-preventable diseases in patients with immunocompromise is to reduce exposure to vaccine-preventable infections. This can be accomplished by vaccinating household members and health care contacts to provide a protected environment for the patient. Immunocompetent individuals who live in a household with a patient with immunocompromise can safely receive all inactivated vaccines, according to the current CDC guideline-recommended vaccination schedule for children and adults.

One area of concern is the administration of live attenuated vaccines to household contacts and health care workers. The risk of viral shedding and transmission of disease is small, but real, and should be considered when determining the best vaccine to give these contacts. After receiving the LAIV, 80% of healthy recipients shed vaccine virus strains for a mean of 7.6 days. Thirty percent of recipients have detectable virus in the nasal secretions after receiving LAIV (Block 2008; Talbot 2005). Still, transmission of the virus to an immunocompromised person has not been documented. With these limited data, it is considered safe to administer LAIV to the household contacts of most patients with immunocompromise, except for HSCT recipients. The other live virus vaccines (MMR, varicella, zoster, rotavirus), even though they may have a viral shedding period and may carry the risk of viral vaccine transmission, have not been shown to transmit symptomatic disease to patients with immunocompromise. Therefore, these vaccines are considered safe for use in household contacts. If infants in a household are receiving standard vaccinations, highly immunocompromised individuals should avoid handling diapers for 4 weeks after vaccination to minimize the risk of exposure.

CONCLUSION

In summary, immunocompromise can result from a variety of medical conditions and pharmacologic interventions. It is imperative that health care teams accurately predict a patient's risk of immunocompromise and identify an appropriate vaccination strategy for these patients to minimize the risk and associated morbidity of vaccine-preventable infectious diseases. Through a thorough evaluation of the available literature and guidelines, clinicians can be prepared to initiate, reevaluate, and modify vaccination plans for individual patients to improve outcomes.

Practice Points

Patients with compromised immune function are at a significantly higher risk of infection, including with vaccine-preventable diseases. Certain patients with immunocompromise should be evaluated to assess whether they require revaccination to afford them the best chance at protection against these diseases.

- **The immune system is made up of innate and acquired immunity. Within acquired immunity, cellular and humoral immunity are the targets of vaccination.**
- **Guidelines regarding the use of vaccinations in patients with immunocompromise have been published by the American Society for Blood and Marrow Transplantation, IDSA, and the American Society of Transplantation.**
- **Data regarding revaccination are strongest in HSCT recipients. In these patients, routine revaccination should begin 3–6 months after transplantation to maximize protection.**
- **Consideration must be given to the specific vaccine formulations and their relative immunogenicity and safety in patients with immunocompromise.**

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Self-Assessment Questions

21. Which one of the following patients is at highest risk of immunocompromise after chemotherapy?

    A. A 35-year-old receiving cisplatin and etoposide for the management of non–small cell lung cancer.
    B. An 18-month-old receiving high dose methotrexate/leucovorin, doxorubicin, cisplatin, and ifosfamide for the management of osteosarcoma.
    C. A 42-year-old receiving cyclophosphamide, vincristine, doxorubicin, and prednisone for the management of non-Hodgkin lymphoma.
    D. A 13-month-old receiving methotrexate, cytarabine, cyclophosphamide, vincristine, doxorubicin, and prednisone for the management of acute lymphoblastic leukemia (ALL).

22. Because of a critical shortage of injectable influenza vaccine, the CDC has suggested the use of live-attenuated influenza vaccine (LAIV) for patients without a contraindication to the vaccine this year. Based on this scenario, which of the following patients would be the most appropriate candidate to receive LAIV?

    A. A 26-year-old patient with HIV infection receiving antiretroviral therapy, with a current $CD4^+$ T-cell count of 380 cells/mm^3
    B. A 54-year-old patient with acute myelogenous leukemia who is 5 months post-allogeneic hematopoietic stem cell transplantation (HSCT)
    C. A 48-year-old patient with cirrhosis who is 3 weeks post-cadaveric liver transplantation
    D. A 39-year-old patient with non-Hodgkin lymphoma who is receiving cycle 3 of chemotherapy

23. A 67-year-old patient is scheduled to receive therapy with rituximab, ifosfamide, carboplatin, and etoposide for the treatment of relapsed non-Hodgkin lymphoma. Which one of the following is the best vaccination strategy for this patient?

    A. Hepatitis B virus (HBV) and zoster vaccines before starting chemotherapy
    B. HBV, pneumococcal, and DTaP vaccines starting 3 months after completing chemotherapy
    C. HBV, DTaP, and pneumococcal vaccines starting 6 months after completing chemotherapy
    D. HBV and DTaP vaccines in between chemotherapy cycles

24. Which one of the following is most likely to be designated a "high-level immunosuppression" clinical scenario?

    A. A 43-year-old HIV-positive patient with no symptoms and a CD4 count of 625 cells/mm^3 receiving combined antiretroviral therapy
    B. A 52-year-old patient with AML after allogeneic HSCT receiving prednisone for treatment of graft-vs.-host disease (GVHD)
    C. A 23-year-old patient who is 3 years after cadaveric renal transplantation receiving maintenance tacrolimus therapy
    D. A 5-year-old patient with ALL receiving maintenance therapy with mercaptopurine

25. A 45-year-old man with non-Hodgkin lymphoma is 6 months after an autologous HSCT. His posttransplant course has been uncomplicated, and he arrives in the clinic for a routine follow-up. Which one of the following vaccination series is best to recommend for this patient?

    A. HBV, DTaP, and IPV vaccines
    B. Hib, MMR, and DTaP vaccines
    C. HBV, Tdap, and PPSV23 vaccines
    D. Zoster, Tdap, and MMR vaccines

26. A 4-year-old patient with ALL presents 16 months after an allogeneic HSCT. His posttransplant course has been complicated by significant chronic GVHD, requiring additional immunosuppression and treatment with high-dose prednisone. His chronic GVHD is still active, and he currently takes 1 mg/kg of prednisone for therapy. He has completed three doses of PCV13 and is due for a fourth dose today. Which one of the following is best to recommend for this patient at this visit?

    A. Administer one dose of PCV13.
    B. Wait until the patient's prednisone dose is less than 20 mg/day; then administer one dose of PCV13.
    C. Wait until the patient's GVHD has resolved and his prednisone dose is less than 20 mg/day; then administer one dose of PPSV23.
    D. Administer one dose of PPSV23.

27. A 48-year-old man with HIV infection is not currently taking combined antiretroviral therapy. He received a three-dose HBV vaccination series, completed 2 months ago. Evaluation revealed an anti-HBs concentration of 6 mIU/mL. Which one of the following is best to recommend for this patient?

    A. Give one dose of double-dose HBV vaccination.
    B. Give long-term therapy with antiviral lamivudine.
    C. Repeat a full three-dose series using a double-dose HBV vaccination.
    D. Give one additional dose of standard-dose HBV vaccination.

28. A 62-year-old woman presents after an autologous HSCT for non-Hodgkin lymphoma. She is 8 months posttransplantation and has not received any posttransplant

vaccinations. Her physician asks about vaccines against whooping cough, in particular. Which one of the following is best to recommend for this patient?

A. Single-dose Tdap booster
B. Single-dose Td
C. Three-dose Tdap series
D. Three-dose DTaP series

Questions 29 and 30 pertain to the following case.

M.M. is a 67-year-old man who presents after an autologous HSCT for multiple myeloma. He is currently 3 years posttransplantation with no active complications. His myeloma continues to be in remission.

29. While in the clinic, M.M. mentions that his primary care provider (PCP) recommended the "shingles vaccine" because he qualifies by age. Which one of the following is best to recommend for M.M.?

    A. Administer the zoster vaccine.
    B. Administer the varicella vaccine.
    C. Administer the zoster vaccine when he is 5 years posttransplantation.
    D. Place him on lifelong valacyclovir prophylaxis.

30. M.M. asks about the "shingles vaccine" for his 66-year-old wife. Which one of the following is the best recommendation for M.M.'s wife?

    A. Administer the zoster vaccine now.
    B. Administer the varicella vaccine now.
    C. Begin acyclovir prophylaxis.
    D. Administer the zoster vaccine, but warn her against contact with her husband for 2 weeks.

31. For which one of the following HSCT recipients would it be best to recommend meningococcal vaccination?

    A. A 19-year-old recipient of an allogeneic HSCT at age 16 who is in college
    B. A 38-year-old recipient of an allogeneic HSCT who is 3 years after transplantation with GVHD
    C. A 67-year-old recipient of an autologous HSCT who is in acute physical rehabilitation for 3 months after transplantation
    D. A 57-year-old military veteran who presents 6 months after an autologous HSCT

32. A 54-year-old patient with multiple myeloma received an autologous HSCT 40 days ago. Many influenza cases have occurred at your institution, so the patient's physician would like to administer a dose of influenza vaccine to the patient. Which one of the following is best to recommend for this patient?

    A. Administer a single dose of the inactivated trivalent influenza vaccine.
    B. Recommend safety precautions and vaccination of family and health care workers.
    C. Administer a single dose of the inactivated high-dose influenza vaccine.
    D. Administer two doses of the inactivated quadrivalent influenza vaccine at least 6 weeks apart.

33. Which one of the following patients has the greatest risk of immunocompromise?

    A. A 9-month-old with a diagnosis of ALL, undergoing induction therapy
    B. A 5-year-old with a diagnosis of ALL, undergoing maintenance therapy
    C. A 19-year-old with a diagnosis of acute myeloid leukemia, undergoing induction therapy
    D. A 34-year-old with a diagnosis of non-Hodgkin lymphoma, undergoing induction therapy

34. Which one of the following is best to recommend for pneumococcal vaccination in a 16-year-old patient with HIV infection?

    A. Two doses of PCV13 separated by 4 weeks
    B. A single dose of PCV13
    C. A single dose of PPSV23
    D. A dose of PCV13 followed by a dose of PPSV23 8 weeks later

35. A 9-year-old patient needs a liver transplant for end-stage liver disease. Which one of the following is the best varicella vaccination dosing recommendation before transplantation?

    A. A single dose of varicella vaccine
    B. Two doses of varicella vaccine
    C. A single dose of zoster vaccine
    D. Two doses of zoster vaccine

36. Which one of the following chemotherapy regimens is most likely to have the most profound impact on a patient's immunity?

    A. Bortezomib, lenalidomide, and dexamethasone for treatment of myeloma
    B. Daunorubicin and cytarabine for treatment of acute myelogenous leukemia
    C. Rituximab and bendamustine for treatment of lymphoma
    D. Cyclophosphamide, paclitaxel, and doxorubicin for treatment of breast cancer

37. A 28-year-old patient who presents 22 months after an allogeneic HSCT currently has grade 2 acute gut GVHD. He takes 40 mg of oral prednisone daily. Which one of the following vaccines is most likely to cause problems if administered to this patient?

    A. IIV (inactivated influenza vaccine)
    B. PPSV23
    C. PCV13
    D. MMR

38. A 47-year-old man presents 5 months after liver transplantation. He received a three-dose series of HBV vaccine at 3, 4, and 5 months posttransplantation, using the 40-mg dose. Which one of the following is best to recommend for this patient?

    A. Check antibody titer and administer 40-mg dose only if titer is low.
    B. Administer a 20-mg booster dose.
    C. Check antibody titer and administer 20-mg dose only if titer is low.
    D. Administer a 40-mg booster dose.

39. A 22-year-old woman presents to her PCP for routine health maintenance. She has HIV infection and is receiving antiretroviral therapy. Her most recent CD4 count was 650 cells/mm^3. Which one of the following vaccines is best to recommend for this patient?

    A. PCV13 for 3 doses
    B. PPSV23 and human papillomavirus (HPV)
    C. PCV13 and HPV
    D. HPV only

40. Which one of the following patients is most likely to have a drop in immunity necessitating revaccination after chemotherapy?

    A. A 34-year-old patient with metastatic breast cancer
    B. A 52-year-old patient with colorectal cancer
    C. A 57-year-old patient with ALL
    D. A 67-year-old patient with multiple myeloma

Learner Chapter Evaluation: Vaccination in the Patient with Immunocompromise.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

20. The content of the chapter met my educational needs.
21. The content of the chapter satisfied my expectations.
22. The author presented the chapter content effectively.
23. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
24. The content of the chapter was objective and balanced.
25. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
26. The content of the chapter was useful to me.
27. The teaching and learning methods used in the chapter were effective.
28. The active learning methods used in the chapter were effective.
29. The learning assessment activities used in the chapter were effective.
30. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

31. Distinguish between innate, adaptive, cellular, and humoral immunity, including the role of the cells involved in each.
32. Assess the impact of diseases and therapies on immunity.
33. Develop a risk-benefit tool to determine the vaccination plan for a particular patient.
34. Using current data and the available vaccines, justify the optimal vaccination product and timing for the patient with immunocompromise.
45. Evaluate opportunities to improve vaccination rates and emerging trends in vaccinations in the patient with immunocompromise.

Questions 36–38 apply to the entire learning module.

36. How long did it take you to read the instructional materials in this module?
37. How long did it take you to read and answer the assessment questions in this module?
38. Please provide any additional comments you may have regarding this module:

Hematologic Care I

Hematologic Care I Panel

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Chronic Lymphocytic Leukemia

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Chronic Lymphocytic Leukemia

By Sol Atienza Yoder, Pharm.D., BCOP

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LEARNING OBJECTIVES

1. Devise appropriate chronic lymphocytic leukemia (CLL) treatments on the basis of patient characteristics.
2. Develop management plans for adverse effects and drug interactions of drug therapy for CLL.
3. Design an antimicrobial prophylaxis regimen based on the drug therapy used for CLL.
4. Construct an appropriate management plan for hepatitis B reactivation with CLL drug therapy.
5. Detect or manage complications commonly experienced by patients with CLL.

ABBREVIATIONS IN THIS CHAPTER

AIHA	Autoimmune hemolytic anemia
Anti-HBc	Hepatitis B core antibody
Anti-HBs	Hepatitis B surface antibody
BTK	Bruton tyrosine kinase
CLL	Chronic lymphocytic leukemia
CMV	Cytomegalovirus
HBsAg	Hepatitis B surface antigen
HBVR	Hepatitis B virus reactivation
ITP	Idiopathic thrombocytopenic purpura
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI3K-J	Phosphoinositide 3-kinase-delta
PJP	*Pneumocystis jiroveci* pneumonia
PRCA	Pure red cell aplasia
RT	Richter transformation
TLS	Tumor lysis syndrome

Table of other common abbreviations.

OVERVIEW OF CHRONIC LYMPHOCYTIC LEUKEMIA

Epidemiology

Chronic lymphocytic leukemia (CLL) is one of the most common forms of leukemia in adults, together with acute myelogenous leukemia (ASH 2016). Chronic lymphocytic leukemia occurs slightly more often in men than in women (Siegel 2016) and is uncommon in children. Chronic lymphocytic leukemia accounts for about 30% of new leukemia cases in the United States annually. The American Cancer Society estimates 18,960 new cases and 4660 deaths from CLL in 2016. The average age at time of diagnosis is 71 years, and less than 12% of diagnoses occur in people younger than 40 (ACS 2016; SEER 2016). According to 2010–2012 data, the Surveillance, Epidemiology, and End Results Program estimates that 0.6% of men and women will receive a diagnosis of CLL during their lifetime (SEER 2016). Risk factors include exposure to chemicals such as Agent Orange (Pesticide Orange) and pesticides, familial history, sex, and ethnicity. First-degree relatives such as parents, siblings, and children have double the risk of having CLL. Those of North American and European descent are more apt to have CLL than is the Asian population. Genetics is thought to play a stronger role than the environment as a risk factor. Asians who reside in the United States have no higher incidence of CLL than Asians who live in Asia (ACS 2016). Studies are ongoing to identify the genes associated with a higher risk of acquiring CLL (Houlston 2002).

Pathogenesis

Chronic lymphocytic leukemia is abnormal growth of B lymphocytes, or WBCs, in the bone marrow. In chronic leukemia, these lymphocytes can partly mature and still appear normal. However, abnormal cells do not function as well as normal cells. The cancer cells have a longer

life span and cause normal lymphocytes to be crowded out of the bone marrow. These abnormal lymphocytes may disseminate in the blood and spread to the lymph nodes, liver, and spleen. Chronic lymphocytic leukemia is a clonal disorder of B lymphocytes characterized by greater than 5000/mm^3 peripheral B lymphocytes having specific cellular markers. A lymph node biopsy reveals normal B cells that are replaced or inhibited by abnormal clones. Other components of the bone marrow are depressed such as the RBCs, platelets, and immunoglobulins. A diagnosis of CLL is typically made when patients visit their local physician for other reasons, such as a routine physical examination. Laboratory tests may reveal elevated WBCs, lymphocyte counts, or both. On presentation, most patients have swollen or palpable lymph nodes, 10% of patients present with B symptoms (fevers, weight loss, night sweats), and 20%–50% of patients present with hepatosplenomegaly (Nabhan 2014). The absence of lymphocytosis despite lymphadenopathy is diagnostic of small lymphocytic leukemia, a pathologically similar disease.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

Normal laboratory values

- Haptoglobin 45–165 mg/dL
- IgG > 500 mg/dL
- LDH 100–210 IU/L
- Lymphocytes (1000–4000/mm^3)
- Reticulocyte count 0.5%–2.5%
- Direct Coombs test: Tests for antibodies that adhere to RBCs and cause early death. If positive test, the cause may be autoimmune hemolytic anemia

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Arnason JE, Brown JR. Targeted therapy for chronic lymphocytic leukemia: current status and future directions. Drugs 2015;75:43-55.
- Combest AJ, Danford RC, Andrews ER, et al. Overview of the recent developments in chronic lymphocytic leukemia, part 1. J Hematol Oncol Pharm 2016;6:54-6.
- Combest AJ, Danford RC, Andrews ER, et al. Overview of the current treatment paradigm in chronic lymphocytic leukemia, part 2. J Hematol Oncol Pharm 2016;6:89-94.

Staging

The Rai and Binet staging methods are used to define CLL status and prognosis. Both methods, first established in the 1970s, are based on physical findings and standard laboratory tests (Table 1-1). Each staging method has three distinct categories associated with prognosis. However, the Rai and Binet staging systems do not fully assess a patient with CLL. Other factors are considered to determine treatment and predict survival.

Treatment Considerations

For most patients, CLL has an indolent course. The decision to "watch and wait" can result in no active treatment for many years. About 25%–50% of patients will be asymptomatic at the time of presentation. Patients with newly diagnosed CLL in early-stage disease without evidence of disease progression or disease-related complications do not warrant active treatment. Treatment of early-stage CLL with alkylating agents versus a "watch-and-wait" method does not result in improved overall survival (OS) (Dighiero 1998). Instead, asymptomatic patients should be closely and regularly monitored for any changes in the disease. As an example, every 3 months, a patient is monitored for history of any new symptoms, physical examination for any new findings, and laboratory value changes. This assesses for disease progression and lymphocyte doubling time. If a patient appears stable for a while, intervals between follow-up can lengthen.

According to 2005–2011 Surveillance, Epidemiology, and End Results Program statistics, the 5-year OS is 81.7% (SEER 2016). About two-thirds of all patients with CLL eventually require active treatment. Treatment is warranted when patients have progressive or symptomatic disease (Box 1-1)

Box 1-1. Evidence of Progressive Chronic Lymphocytic Leukemia

- Marrow failure with worsening cytopenias (anemia and/or thrombocytopenia)
- Progressive lymphocytosis (a lymphocyte increase > 50% in 2 mo or doubling time < 6 mo)
- Massive or progressive splenomegaly (> 6 cm below left costal margin)
- Massive or progressive lymphadenopathy (at least 10 cm)
- Treatment-refractory autoimmune cytopenias
- Significant B symptoms:
  - Significant fatigue
  - Persistent temperatures > 100.5°F (38°C) for at least 2 wk
  - Night sweats for > 1 mo without evidence of infection
  - Unintentional weight loss of at least 10% in previous 6 mo

Information from: Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood 2008;111:5446 [Abstract]; and Nabhan C, Rosen ST. Chronic lymphocytic leukemia. A clinical review. JAMA 2014;312:2265-75.

Table 1-1. Rai and Binet Stages for Chronic Lymphocytic Leukemia

Stage	Clinical Features	Median Survival (yr)[a]
Low risk Rai = Stage 0 Binet = Stage A	**Rai Stage** • Lymphocytosis with leukemia cells in peripheral blood (> 15,000/mm^3) and/or bone marrow (> 40%) **Binet Stage** • Up to two areas of lymphadenopathy[b]	10
Intermediate risk Rai = Stage I/II Binet = Stage B	**Rai Stage** • Lymphocytosis plus lymphadenopathy, hepatomegaly/splenomegaly, or both **Binet Stage** • Three or more areas of lymphadenopathy[b]	8
High risk Rai = Stage III/IV Binet = Stage C	**Rai Stage** • Lymphocytosis plus anemia (Hgb < 11 g/dL), thrombocytopenia (Plt < 100,000/mm^3), or both **Binet Stage** • Anemia, thrombocytopenia, or both	6.5

[a]Reflects statistics before newer and targeted therapies. Median survival is defined as years from diagnosis to when 50% of population had survived.

[b]Nodal areas: cervical, axillary, inguinal (one side or both), spleen, and liver.

Information from: Nabhan C, Rosen ST. Chronic lymphocytic leukemia. A clinical review. JAMA 2014;312:2265-75; Zelenetz AD, Gordon LI, Wierda WG, et al. National Comprehensive Cancer Network Guidelines, version 1, 2017. Chronic lymphocytic leukemia/small lymphocytic lymphoma; and Cancer Research United Kingdom. Survival Statistics for Chronic Lymphocytic Leukaemia (CLL), 2013.

or are in advanced stages (Rai III and IV or Binet stage C). Advanced stages account for about 25% of patients with newly diagnosed CLL (Table 1-2). In Rai stage I/II or Binet stage B, active treatment may not be warranted, and the patient can be observed for progressive or symptomatic disease (Hallek 2008).

When evaluating these signs, practitioners should be careful not to focus on the absolute number alone, but to consider the rate of disease progression such as the lymphocyte doubling time.

Drug therapy selection for CLL is based on several characteristics including cytogenetics, age, comorbidities, the patient's performance status, response to previous treatments, and likely prognosis. Currently, molecular cytogenetics is one of the most important indicators of prognosis (Table 1-3). Chromosomal abnormalities are measured by fluorescence in situ hybridization analysis, polymerase chain reaction, peripheral blood, or flow cytometry. These chromosomal abnormalities occur in 50%–80% of patients with CLL (Döhner 2000) and are associated with a good, intermediate, or poor prognosis. Furthermore, these cytogenetic abnormalities may play a more primary role in treatment selection. The International Prognostic Index for Patients with Chronic Lymphocytic Leukemia Working Group has created a prognostic model that identifies four distinct CLL risk groups: low, intermediate, high, and very high risk. This tool integrates prognostic markers such as gene mutations and biological characteristics. This model is based on five parameters: TP53 mutations (17p and TP53), immunoglobulin heavy-chain variable region mutational status (mutated vs. unmutated), β_2-microglobulin concentration (cutoff 3.5 mg/L), clinical stage (Rai/Binet), and age (cutoff at age 65) (International CLL-IPI Working Group 2016). Further testing is needed through clinical trials to validate this prognostic model and, hopefully, allow a more targeted approach to treating patients with CLL.

Table 1-2. Stage of Patients with Chronic Lymphocytic Leukemia at Diagnosis

Rai stage	0	I/II	III/IV
Binet	A	B	C
Patients at diagnosis	25%	50%	25%

Information from: Gribben JG. How I treat CLL up front. Blood 2010;115:187-97.

Table 1-3. Molecular Markers in Chronic Lymphocytic Leukemia

Molecular Marker	Frequency (%)	Prognostic Significance	Test Method
Deletion 13q	32–50	Good	FISH
Trisomy 12	11–20	Intermediate	FISH
Deletion 11q	16–20	Poor	FISH
Deletion 17p	10–20	Poor (most)	FISH
Unmutated IGHV	54	Poor	PCR
β_2 microglobulin > 3.5 mg/L	25	Poor	Blood
70-kDa zeta-associated protein (ZAP-70) ≥ 20% expression	38	Poor	Flow cytometry
CD38 ≥ 30% expression		Poor	Flow cytometry

FISH = fluorescence in situ hybridization; IGHV = immunoglobulin heavy-chain variable region; PCR = polymerase chain reaction.

Information from: Zelenetz AD, Gordon LI, Wierda WG, et al. National Comprehensive Cancer Network Guidelines, version 1, 2017. Chronic lymphocytic leukemia/small lymphocytic lymphoma; Pflug N, Bahlo J, Shanafelt TD, et al. Development of a comprehensive prognostic index for patients with chronic lymphocytic leukemia. Blood 2014;124:49-62; and Gribben JG. How I treat CLL up front. Blood 2010;115:187-97.

Clinical trials and large referral centers generally do cytogenetic testing before initiating treatment. At diagnosis, however, the identification of poor prognostic factors does not affect the treatment plan of an asymptomatic patient with CLL, so some controversy exists regarding whether up-front molecular cytogenetic testing is necessary. Some would argue that obtaining cytogenetics on diagnosis facilitates appropriate patient counseling and closer monitoring in patients with high-risk markers (Brown 2015). Even if no abnormalities are identified at diagnosis, upon relapse or change of treatment, cytogenetic testing should be repeated before starting therapy due to the cytogenetic evolution potential. Selection of treatment for CLL with molecular profiling is not standard, except for deletion 17p [del(17p)], or loss of the short arm on chromosome 17 (Gribben 2010). The del(17p) lacks part of the chromosome that suppresses cancer growth (FDA 2016). The del(17p) signifies a high risk of disease progression with a shorter expected survival than with the other cytogenetic abnormalities. The del(17p) is associated with the worst prognosis of all chromosomal abnormalities and takes precedence in patients with more than one abnormality.

The incidence of del(17p) in untreated patients with CLL is 10% (FDA 2016). However, disease evolution and ongoing treatment increases the risk of acquiring del(17p). The incidence of del(17p) in patients with relapsed CLL is 20% (FDA 2016).

NEWER DRUGS

In the past 2 decades, survival has increased for younger patients but has remained unchanged for older adults (Abrisqueta 2009; Brenner 2008). Increased survival occurred in the first 5 years after diagnosis in the younger population compared with the older adult population with CLL. This may be because of newer and more effective therapies. As the understanding of CLL biology deepens, treatment options have expanded and are better understood. However, traditional chemoimmunotherapy, including CD20-specific monoclonal antibodies, purine analogs, and alkylating agents, remains standard of care for many patient groups. Newer oral agents may provide an expanded treatment option for the frail and older adults. This chapter reviews the place in therapy for newer oral agents, including ibrutinib, idelalisib, and venetoclax.

Ibrutinib

Place in Therapy

Ibrutinib is the first selective irreversible Bruton tyrosine kinase (BTK) inhibitor to be FDA approved for the treatment of CLL and first line for CLL with del(17p).

Mechanism of Action

Bruton gets its name from a rare congenital disease called Bruton agammaglobulinemia that is characterized by agammaglobulinemia, absence of mature B cells, and mutation

in the *BTK* gene (Sanford 2015). Bruton tyrosine kinase is required for normal B-cell function and development. Bruton tyrosine kinase targets intracellular signaling pathways, which are further down from the B-cell receptor and are essential for activating several tumor-cell survival pathways in CLL. Ibrutinib inhibits BTK, thus preventing proliferation of malignant B cells and improving survival.

A multicenter, open-label, phase III study evaluated 373 patients with relapsed and refractory CLL. Patients received ibrutinib 420 mg orally daily or ofatumumab, intravenously starting at 300 mg at week 1 and titrated according to product labeling. Patients were stratified by resistance to purine analog–based chemoimmunotherapy and presence of del(17p). The overall response rate (ORR) favored ibrutinib over ofatumumab (42.6% vs. 4.1%, p<0.001). Overall survival at 12 months was 90% in the ibrutinib group compared with 81% in the ofatumumab group. A subset of patients with del(17p) had a median progression-free survival (PFS) at 6 months of 88% in ibrutinib patients (n=32) compared with 65% in ofatumumab patients (n=33) (Byrd 2014). U.S. Food and Drug Administration approval was granted for patients with del(17p). A phase Ib/II multicenter study of two fixed doses of ibrutinib, 420 mg and 840 mg, showed that response was similar, regardless of whether the del(17p) abnormality was present (68% vs. 71%) (Byrd 2013).

Approval for use as first-line therapy in all patients with CLL is based on an international, randomized, open-label, phase III study of untreated older adult patients with CLL. The trial compared ibrutinib 420 mg orally once daily with chlorambucil 0.5 mg/kg (maximum titration to 0.8 mg/kg) orally on days 1 and 15 of a 28-day cycle for up to 12 cycles (Burger 2015). The primary study end point of PFS was significantly longer in the ibrutinib group than in the chlorambucil group (median not reached vs. 18.9 months). Other end points such as OS, relative risk of death, ORR, and sustained increases from baseline values of hemoglobin and platelet values were better in the ibrutinib group. Furthermore, an analysis of this trial evaluated dose intensity (DI), defined as the proportion of actually administered versus planned doses. This showed that patients with a higher DI or greater adherence had longer PFS, regardless of cytogenetic abnormalities (Barr 2015).

The starting dose for ibrutinib is 420 mg orally once daily until disease progression or unacceptable toxicity. It is available in 140-mg capsules. Ibrutinib package labeling states that in mild liver impairment (Child-Pugh class A), the recommended dose is 140 mg. Because ibrutinib is metabolized by the liver, use in moderate (Child-Pugh class B) and severe (Child-Pugh class C) disease is not recommended.

Adverse Effect Profile

The most common adverse effects include diarrhea (42%), fatigue (30%), cough (22%), nausea (22%), rash (21%–25%), and peripheral edema (19%) (Burger 2015). Less common toxicities and more severe disease–grade 3 or greater using Common Terminology Criteria for Adverse Events version 4.0–include neutropenia (WBC less 2000/mm^3) (10%), anemia (hemoglobin less than 8 g/dL) (6%), bleeding events (GI bleed, hematuria, postprocedural bleeding, intracranial hemorrhage, subdural hematoma) (6%), atrial fibrillation and flutter (6%–9%), and hypertension (systolic blood pressure of 160 mm Hg or greater or diastolic blood pressure of 100 mm Hg or greater) (4%).

Monitoring Values

Transient lymphocytosis is a hallmark of B-cell receptor antagonists, including ibrutinib. This is thought to be caused by rapid shrinkage of lymph nodes and demargination of lymphocytes from these lymph nodes into the peripheral blood (Molica 2015). Onset is typically within the first 2 weeks of therapy, and disease peaks at a median of 4 weeks. Duration can be as long as several months while on treatment. In most patients, transient lymphocytosis is self-limiting and can resolve on its own within 8–12 months. This condition should not be considered progressive disease unless accompanied by worsening lymphadenopathy, anemia, thrombocytopenia, hepatosplenomegaly, or B symptoms (Cheson 2012). Do not discontinue ibrutinib without evidence of disease progression because the progression rate may increase after withdrawal. Prolonged lymphocytosis, greater than 12 months, has been associated with favorable prognostic characteristics such as mutated immunoglobulin heavy-chain variable region and del(13q). Furthermore, patients who have responded to ibrutinib have also had persistent lymphocytosis (Woyach 2014a; Woyach 2014b).

The cause of bleeding associated with ibrutinib, though not fully understood, is postulated to be because of decreased platelet adhesion and aggregation by inhibition of collagen and von Willebrand factor (Molica 2015). The degree of reduction in collagen response may correlate with the occurrence of bleeding. Patients concomitantly taking warfarin had initial episodes of intracranial bleeding. The current recommendation is not to administer warfarin or other antiplatelet drugs (aspirin, clopidogrel) concomitantly with ibrutinib (Kamel 2015). Patients should be monitored closely for bleeding. If bleeding occurs, a medication profile review should be done to isolate all offending agents, and consideration should be given to discontinue ibrutinib. If clinically necessary, platelet transfusions may be administered (Kamel 2015).

Because ibrutinib is associated with atrial fibrillation and flutter, patients should be monitored regularly for arrhythmias. According to product labeling, patients with cardiac risk factors such as hypertension, acute infections, or a history of atrial fibrillation should be monitored. If clinically indicated, thromboprophylaxis with anticoagulants or antiplatelet agents may be considered. However, ibrutinib should be used with caution when given concomitantly with warfarin, other

anticoagulants, or antiplatelet medications because ibrutinib may enhance the anticoagulant and antiplatelet properties (Zelenetz 2017). As mentioned earlier, ibrutinib can also be associated with bleeding tendencies. If this becomes a factor, the risk-benefit must be weighed. If the recurrent atrial fibrillation is not medically controlled, patients can be changed to idelalisib (Zelenetz 2017).

Because of the bleeding risks with ibrutinib, it should be held for 7 days before and after any major surgery (e.g., total knee replacement). For minor surgical procedures, ibrutinib should be held for 3 days before and 3 days after surgery (Zelenetz 2017). Rash appears in two subtypes: (1) a nonpalpable, asymptomatic petechial rash; and (2) a palpable eruption with pruritic, nonblanching, purpuric papules. Median onset of rashes after the first ibrutinib dose occurred in 80 days and 15 days, respectively. While the nonpalpable rash requires no therapy, the palpable rash can be treated with oral antihistamines, and systemic and topical corticosteroids. Ibrutinib is discontinued and resumed following resolution of palpable rash (Iberri 2015). Ibrutinib-associated hypertension is uncommon. Usually, ibrutinib-induced hypertension can be managed with antihypertensives. If the hypertension is uncontrollable, ibrutinib should be discontinued.

Drug Interactions

Drug-drug and drug-food interactions must be considered with this agent (Table 1-4). Ibrutinib is metabolized primarily by CYP3A enzymes. Management of use of strong or moderate CYP3A inhibitors with ibrutinib can depend on the duration of concomitant administration. Grapefruit, grapefruit juice, and Seville oranges should also be avoided because of their moderate inhibition of CYP3A enzymes.

Idelalisib

Place in Therapy

Idelalisib is approved in combination with rituximab for patients with relapsed or refractory CLL who are ineligible for chemotherapy because of significant comorbidities.

Mechanism of Action

Idelalisib is an inhibitor of the delta isoform of phosphoinositide 3-kinase delta (PI3K-δ). There are several isoforms of PI3Ks (p110α, p110β, 110γ, p110δ), of which PI3K-δ is most associated with CLL. The PI3Ks convert phosphatidylinositol-(4,5)-biphosphate to phosphatidylinositol-(3,4,5)-triphosphate ($PtdInsP_3$), which provides a binding site for enzymes. One of the most important enzymes is the serine/threonine kinase (AKT/PKB). The AKT/PKB plays an important role in metabolism, growth, cell proliferation, and survival. Bruton tyrosine kinase, which can be found on B cells, is an important mediator of PI3K signaling. Activated PI3K-δ mediates signaling through these B-cell receptors (Herman 2010; Okkenhaug 2003). Inhibition of PI3K-δ by idelalisib results in inhibition of signaling pathways, which prohibits proliferation in cell lines and induces apoptosis.

Rituximab plus idelalisib or placebo was studied in 220 patients with high-risk features such as del(17p), del(11q), or unmutated immunoglobulin heavy-chain variable region. The ORR in the idelalisib arm was 81%, all of which were partial responses, compared with 13% in the placebo group. Median PFS was not reached; however, the 24-week PFS favored idelalisib at 93% compared with 46% in the placebo arm. One-year OS was 92% and 80%, respectively (Furman 2014).

In March 2016, a drug warning for idelalisib was distributed regarding decreased OS and increased risk of serious

Table 1-4. Ibrutinib Drug Interactions

CYP3A Action	Examples	Usage	Action Plan
Drugs: strong inhibitors	Ketoconazole, clarithromycin, itraconazole, posaconazole, voriconazole	Short-term (≤ 7 days)	Consider interrupting ibrutinib while using the inhibitor
		Long-term	Avoid concomitant use
Drugs: moderate inhibitors	Erythromycin, ciprofloxacin, fluconazole	Short-term (≤ 7 days)	Consider interrupting ibrutinib while using the inhibitor
		Long-term	Decrease ibrutinib dose to 140 mg daily. Monitor closely for signs of ibrutinib toxicity
Foods: moderate inhibitors	Grapefruit products, Seville oranges		Avoid concomitant use
Drugs: strong inducers	Carbamazepine, phenytoin, rifampin, St. John's wort		Avoid concomitant use. Consider alternative agents with less CYP3A induction

Information from manufacturer's package inserts; and Vela CM, McBride A, Jaglowski SM, et al. Ibrutinib for treatment of chronic lymphocytic leukemia. Am J Health Syst Pharm 2016;73:367-75.

infections in patients receiving idelalisib (HSA 2016). Three phase III studies showed increased rates of serious adverse effects and decreased OS. Most of these adverse effects were infections, including sepsis and pneumonia. Recommendations included administering *Pneumocystic pneumoniae* prophylaxis, monitoring for cytomegalovirus (CMV), discontinuing idelalisib if there are signs of infection or viremia (positive PCR or antigen test), and monitoring blood counts at least every 2 weeks for the first 6 months of therapy and at least weekly if the absolute neutrophil count is less than 1000 cells/mm^3.

Idelalisib is dosed at 150 mg orally twice daily until disease progression or unacceptable toxicity. It is available in 100- and 150-mg tablets. An advantage of idelalisib is that dose adjustment is not necessary in patients with a CrCl as low as 15 mL/minute/1.73 m^2, according to product labeling.

Adverse Effect Profile

Common toxicities include neutropenia (60%), elevations in AST and ALT (38%), fever (32%), anemia (28%), fatigue (26%), nausea (26%), chills (24%), diarrhea (21%), and thrombocytopenia (19%). Severe toxicities of grade 3 and greater include pneumonia (7%), pyrexia (7%), and febrile neutropenia (5%) (Furman 2014). Treatment interruptions occurred in 3.6% of patients, with dose reduction warranted in 1.3% of patients receiving this drug (Shah 2015). Idelalisib administration requires a REMS (Risk Evaluation and Mitigation Strategies) program to address the serious or fatal risks and management of boxed warnings, including hepatotoxicity, diarrhea/colitis, pneumonitis, and intestinal perforation.

Monitoring Parameters

Liver function test abnormalities usually occur within the first 8–16 weeks of treatment (Furman 2014). Liver function tests should be done at baseline and every 2 weeks for the first 3 months, every 4 weeks for the next 3 months, and every 1–3 months thereafter, or as clinically necessary. According to product labeling, weekly monitoring should occur if ALT or AST concentrations exceed 3 times the upper limit of normal. If AST or ALT concentrations increase to 5 to 20 times the upper limit of normal, idelalisib should be temporarily interrupted. Weekly monitoring should occur until liver function tests normalize. Reinitiating idelalisib at a lower dose (100 mg twice daily) can be considered (Zelenetz 2017). Permanent discontinuation of idelalisib is warranted when ALT/AST is greater than 20 times the upper limit of normal.

Two types of diarrhea are associated with idelalisib (Shah 2015). The first type is mild to moderate and occurs within the first 8 weeks. It is usually controlled with conventional antidiarrheal therapy and diet adjustments. The second type of diarrhea is watery and typically occurs later, with sudden or gradual onset. This variant usually is poorly responsive to antidiarrheals. If diarrhea is refractory grade 2 (increase of less than 4 stools per day) or grade 3 or 4 (increase of more than 4 stools per day), idelalisib should be discontinued, and an oral corticosteroid such as budesonide 9 mg by mouth daily can be initiated. Intravenous steroids equivalent to prednisone 1 mg/kg/day can also be used (Shah 2015). Unless the diarrhea is persistent, idelalisib can be reinitiated at a reduced dose of 100 mg by mouth twice daily once the diarrhea has subsided (Zelenetz 2017; Shah 2015). Idelalisib should be discontinued in severe cases.

Idelalisib-induced pneumonitis/pneumonia is associated with symptoms such as cough, dyspnea, and hypoxia. If chest radiography reveals bilateral pulmonary interstitial infiltrates, discontinue idelalisib immediately. Corticosteroids and/or antibiotics may be considered, depending on the etiology. Some reports suggest that this pneumonitis is similar to the drug-induced pneumonitis associated with mammalian target of rapamycin inhibitors (Shah 2015).

As discussed with ibrutinib, idelalisib can be associated with transient lymphocytosis. Management and considerations of lymphocytosis are similar to ibrutinib. When rituximab is added, the idelalisib-associated lymphocytosis is blunted and shortened in duration compared with single-agent idelalisib (Furman 2014). This is thought to be the result of B-cell depletion by rituximab.

Drug Interactions

Idelalisib is a major substrate of CYP3A4 and a strong inhibitor of CYP3A4. Concomitant administration with strong CYP3A inhibitors or inducers can increase or decrease the AUC of idelalisib by up to 80%, respectively. Concomitant use with idelalisib should be avoided, if possible (Do 2016) (Table 1-5).

Venetoclax

Place in Therapy

Venetoclax, formerly known as ABT-199, induces a high response rate that is durable in patients with relapsed and refractory CLL (Roberts 2015; Seymour 2014). Venetoclax received FDA approval on April 11, 2016, for the treatment of patients with CLL and del(17p) who had received at least one prior therapy.

Mechanism of Action

Venetoclax is a second-generation B-cell CLL/lymphoma 2 (BCL2) antagonist. The BCL2 protein produces an antiapoptotic effect on CLL cells. Increased expression of the BCL2 protein on CLL cells creates resistance to apoptosis, or programmed cell death. This results in accumulation of clonal CLL lymphocytes. Venetoclax blocks BCL2 activity, leading to CLL cell death, and restores the normal apoptotic process (Cimmino 2005).

Approval was based on the multicenter, phase II, single-agent study of 106 patients with CLL and del(17p) who had received at least one prior therapy. This study's ORR was 80%. Median duration of response was not reached after a

Table 1-5. Idelalisib Drug Interactions

Mechanism of Action	Example Medications	Action Plan
CYP3A substrates	Midazolam, buspirone, lovastatin, sildenafil, simvastatin	Avoid concomitant use Consider interrupting idelalisib during the use of the substrate Substrate AUC increases
Strong CYP3A inducers	Carbamazepine, phenytoin, rifampin, St. John's wort	Avoid concomitant use Idelalisib AUC decreases
CYP3A inhibitors	Ketoconazole, clarithromycin, itraconazole, posaconazole, voriconazole, midazolam	Monitor for signs of idelalisib toxicities Follow labeling dose modifications for adverse effects

Information from manufacturer's package inserts; and Do B, Mace M, Rexwinkle A, et al. Idelalisib for treatment of B-cell malignancies. Am J Health Syst Pharm 2016;73:547-55.

median follow-up of about 12 months. Duration of response was from 2.9 months to more than 19 months (ClinicalTrials.gov 2016a, 2016b).

Venetoclax initial dosing is 20 mg orally for 7 days, followed by 1 week at each dose level of 50 mg, 100 mg, and 200 mg; then, the recommended dose is 400 mg orally daily until disease progression or unacceptable toxicity. Stepwise dosing for the first month is available as a convenient dose pack. Venetoclax should be taken with meals.

Adverse Effect Profile

Analyses of safety data for 240 previously treated patients given single-agent venetoclax at a target dose of 400 mg showed the following adverse effects with at least a 20% incidence: neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Serious adverse effects associated with at least a 2% incidence were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and tumor lysis syndrome (TLS).

Monitoring Parameters

Tumor lysis syndrome is a potential oncologic emergency caused by tumor cell lysis and release of potassium, phosphate, and other cell constituents. This solute load can lead to metabolic abnormalities and renal insufficiency if not managed properly. This syndrome is most common after the treatment of lymphomas and leukemias. Life-threatening TLS can occur, given that venetoclax can rapidly decrease the lymphocyte count as early as 6–8 hours after the first dose and at each dose increase. The risk of TLS is a continuum of tumor burden and comorbidities, but patients with any degree of tumor burden may have TLS within the initial 5-week dose titration phase of venetoclax. Patients should be stratified by risk and treated according to the package insert recommendations, including prophylaxis with hydration, anti-hyperuricemics, frequent laboratory monitoring, correction of electrolyte abnormalities, and consideration of dose modifications for toxicities. For high tumor burden (one lymph node of at least 10 cm or a lymph node greater than 5 cm with an absolute lymphocyte count of 25,000/mm^3 or higher), hospitalization may be required for aggressive TLS management. Other factors such as decreased renal function (CrCl less than 80 mL/minute/1.73 m^2) and concomitant use of strong or moderate CYP3A inhibitors and P-glycoprotein inhibitors can increase venetoclax exposure and increase the risk of TLS. If TLS occurs, venetoclax should be held and may require dose adjustments if resumed.

Drug Interactions

Venetoclax is predominantly metabolized by CYP3A4/5. Product labeling states the dose modifications of venetoclax required when given concomitantly with CYP3A4 inhibitors and inducers (Table 1-6). Concomitant administration of venetoclax and warfarin results in an increase in serum concentrations; however, this combination can be managed by monitoring the INR and adjusting warfarin doses accordingly.

Including the agents listed earlier, oral antineoplastic therapy provides treatment options after at least one prior treatment for CLL. Ibrutinib is the only exception that is indicated for first-line therapy. Which therapy to consider selecting first is not known; however, patient characteristics, drug interactions, and cost should be considered.

FUTURE THERAPIES

Acalabrutinib

Acalabrutinib is a more selective, irreversible BTK inhibitor than ibrutinib for the treatment of CLL. A phase I–II multicenter study involved patients with CLL who had been treated with a median of three previous therapies. Thirty-one percent of patients had chromosome del(17p), among whom the ORR was 100%. All patients had an ORR of 95%, with the remaining 5% having stable disease (Byrd 2016).

Table 1-6. Venetoclax Drug Interactions

Mechanism of Action	Example Drugs	Action Plan
Strong CYP3A inhibitor	Ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole	At initiation and during dose titration phase, contraindicated On steady state after dose titration phase, reduce venetoclax dose by at least 75% Resume venetoclax dose that was used before initiating the CYP3A inhibitor 2–3 days after discontinuing the inhibitor
Moderate CYP3A inhibitor P-gp inhibitor	Erythromycin, ciprofloxacin diltiazem, dronedarone, fluconazole, verapamil Or Amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor	Consider alternative treatments If it must be used, reduce steady-state venetoclax dose by at least 50%. Monitor patients more closely for toxicities Resume venetoclax dose that was used before initiating the CYP3A or P-gp inhibitor 2–3 days after discontinuing the inhibitor
Foods that contain CYP3A inhibitors	Grapefruit products, Seville oranges, starfruit	Avoid concomitant use
Strong CYP3A inducers	Carbamazepine, phenytoin, rifampin, St. John's wort	Avoid concomitant use
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Consider alternative treatments with less CYP3A induction
Warfarin	18%–28% increase in warfarin Cmax and AUC	Monitor INR

P-gp = P-glycoprotein.
Information from manufacturer's package inserts.

Because of the selectivity for the target BTK, it avoids the other targets that can lead to adverse effects in patients receiving ibrutinib (Byrd 2015). Unlike ibrutinib, acalabrutinib was not associated with major hemorrhage, atrial fibrillation, TLS, or pneumonitis. Most common adverse effects were grade 1 or 2. These included headache (43%), diarrhea (38%), increased weight (25%), and upper respiratory tract infection (23%). Severe diarrhea, rash, arthralgia or myalgia, bruising, and bleeding events each occurred in 2% or less of patients (Byrd 2016).

Acalabrutinib may be better at treating fast-growing tumors because of its selectivity and short half-life. Because BTK turns over about every 24 hours or less, dosing more often and with a more selective inhibitor could be a more effective treatment strategy. This addition to the BTK inhibitor class of drugs is important when patients cannot tolerate the adverse effects of one BTK inhibitor; therefore, trials have compared acalabrutinib with ibrutinib (NCT 02477696). Combination therapy with other classes of drugs like acalabrutinib and pembrolizumab are undergoing investigation (Clinicaltrials.gov NCT 02362035).

Other Investigational Agents

Duvelisib is also being studied in patients with CLL (Balakrishnan 2015). Duvelisib is an oral second-generation PI3K-J and PI3K-g. Because of its specificity for two PI3K isoforms, it avoids normal cells and minimizes adverse effects. Current studies include combinations with ofatumumab, fludarabine/cyclophosphamide/rituximab, rituximab, obinutuzumab, and venetoclax.

Other investigational agents include entospletinib, an oral selective inhibitor of spleen tyrosine kinase (Syk). Syk is a nonreceptor cytoplasmic, B-cell receptor associated enzyme that is overexpressed in hematopoietic malignancies. Dinaciclib is an intravenous novel cyclin-dependent kinase inhibitor that is active in patients with relapsed CLL (Flynn 2015; Sharman 2015).

Efforts are being made to identify optimal combination regimens and sequence of administration. The unique mechanism of action of newer and upcoming agents can provide drug combinations to attack tumor cells in many ways and may lead to long-term survival and long-term treatment-free periods.

Patient Care Scenario

A 62-year-old woman (height 65 inches, weight 64 kg) presents with complaints of weakness, fatigue, and shortness of breath with minimal exertion. Adenopathy is present. The patient is initiated on ibrutinib 420 mg by mouth once daily.

Day	Baseline	2 Wk	3 Wk
Hgb (female 12–16 g/dL)	5	7.1	9.4
Lymphocytes (1000–4000/mm^3)	11,000	65,000	68,000

On examination, the patient has no signs or symptoms of recurrent or progressive disease. At 3 weeks, upon examination, adenopathy has resolved, and the patient is completely asymptomatic. What is best to recommend to address this patient's lymphocytosis?

ANSWER

At 2 weeks, there is evidence of lymphocytosis. This is the typical time interval of onset for B-cell receptor antagonist–associated lymphocytosis. To assess whether the lymphocytosis is caused by ibrutinib or by the disease, other signs and symptoms must be assessed (see Box 1-1). The patient is asymptomatic, adenopathy is resolved, and the anemia appears to be improving. With an isolated lymphocytosis, the patient can continue ibrutinib with continued monitoring.

1. Woyach J, Smucker K, Smith LL, et al. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood 2014;123:1810-7.
2. Herman SEM, Niemann CU, Farooqui M, et al. Ibrutinib-induced lymphocytosis in patients with chronic lymphocytic leukemia: correlative analyses from a phase II study. Leukemia 2014;28:2188-96.

COMPLICATIONS OF CLL AND MANAGEMENT

When a patient has symptoms but the lymphocyte count and physical examination suggest stable disease, the patient should be evaluated for complications of CLL. For example, changes in WBC counts, but absence of anemia or thrombocytopenia, can suggest possible infection or a medication-induced issue. Several complications of CLL have been described. Identifying these disease states and managing them appropriately is essential.

Infections

Infection is a major cause of morbidity and mortality in patients with CLL. The incidence is 30%–50% (Nosari 2012; Molica 1994), and the pathogenesis is multifactorial, including immunosuppression caused by the disease and effects from the treatment of CLL. Most infections are attributed to the late stages of disease (Perkins 2002; Tsiodras 2000; Molica 1994). Infection in Benet stage A has an incidence of 33% and is not as severe or common as that of patients in stage C, with an infection incidence of 82% (Itala 1992).

The disease process of CLL involves abnormal cellular and humoral-mediated immunosuppression that worsens in later stages and longer duration of the disease (Nosari 2012). As CLL progresses, patients are more prone to infection caused by bone marrow infiltration (Molica 1994). Furthermore, almost all patients with CLL have hypogammaglobulinemia. This is related to deficient T- and monoclonal CD5 B-cell function and correlates with advancement of disease, incidence of infection, and survival (Morrison 2009).

Infections in the patient with CLL also occur because of treatment effect. Chemotherapy, immunotherapy, and targeted oral agents have different immunosuppressive effects on cell-mediated immunity. This results in an array of infections that have changed over the past several decades as treatments have evolved (Table 1-7).

Prophylaxis

Anti-infective prophylaxis is based on extrapolated recommendations from treatment studies and anecdotal evidence. No randomized clinical trials or guidelines address antimicrobial prophylaxis in patients with CLL. Considerations for prophylaxis include whether a patient is treatment naive or heavily treated, planned treatment approach, antimicrobial effects on the immune system, end-organ function, and history of infection (Table 1-8). In addition, medication combinations can increase or prolong the risk of infection compared with medications given separately. This should also be considered.

Purine analogs such as fludarabine, cladribine, and pentostatin result in prolonged suppression of the CD4$^+$ cell count and, to a lesser extent, the CD8$^+$ or natural killer cells. The median CD4$^+$ T lymphocytes are decreased to less than 200/mL within 2–3 months of treatment (Nosari 2012). This suppression can continue up to 1–2 years after therapy is discontinued (Morrison 2009; Morrison 2001). The hematologic effects of purine analogs increase the risk of atypical or unusual opportunistic infections such as *Listeria* and *Pneumocystis* (Morrison 2001). It is reasonable to use antipneumocystis and antiviral prophylaxis, given the approaches used in

Table 1-7. Drug Class and Associated Pathogens

Drug Class	Mechanism of Immunodeficiency	Infections
Alkylating agents/steroids	Mainly originates in mucosa, especially the respiratory tract Fungal and viral less common	*S. pneumoniae* *S. aureus* *P. aeruginosa* *H. influenzae* *E. coli* *K. pneumoniae* *P. jiroveci* Herpes virus
Purine analogs (fludarabine, cladribine, pentostatin)	Bacterial infections are common Opportunistic infections because of T-cell immunosuppression	*Mycobacteria* *P. jiroveci* *Candida* spp. *Aspergillus* spp. Herpes virus
Anti-CD20 monoclonal antibody (rituximab, obinutuzumab, ofatumumab)	Suppressive effects on the B-, T-, and NK cells Neutropenia	Hepatitis B reactivation Herpes virus[a] *P. jiroveci*[a]
Anti-CD52 monoclonal antibody (alemtuzumab)	Suppressive effects on the B and T lymphocytes, monocytes, macrophages, and eosinophils Low CD4 cell counts	*P. jiroveci* Herpes zoster CMV reactivation Hepatitis B reactivation *Legionella*
Phosphatidylinositol 3-kinase inhibitor (idelalisib)	Unknown	*P. jiroveci* CMV

[a]In combination with glucocorticosteroids.

CMV = cytomegalovirus; NK = natural killer.

Information from: Zelenetz AD, Gordon LI, Wierda WG, et al. National Comprehensive Cancer Network Guidelines, version 1, 2017. Chronic lymphocytic leukemia/small lymphocytic lymphoma; Morrison VA. Infectious complications in patients with chronic lymphocytic leukemia: pathogenesis, spectrum of infection, and approaches to prophylaxis. Clin Lymphoma Myeloma 2009;9:365-70; Morrison VA, Rai KR, Peterson BL, et al. Impact of therapy with chlorambucil, fludarabine, or fludarabine plus chlorambucil on infections in patients with chronic lymphocytic leukemia. J Clin Oncol 2001;19:3611-21; and Tsiodras S, Samonis G, Keating MJ, et al. Infection and immunity in chronic lymphocytic leukemia. Mayo Clin Proc 2000;75:1039.

contemporary CLL clinical trials (Nabhan 2014). *Pneumocystis jiroveci* pneumonia (PJP) incidence is up to 7% in patients receiving fludarabine (Anaissie 1998). Sulfamethoxazole/trimethoprim 1 double-strength tablet orally three times weekly may be given until at least 2 months after completing fludarabine treatment. Herpes prophylaxis with acyclovir 400 mg orally twice daily is usually used in patients receiving fludarabine. If the patient has a history of herpetic infections, an acyclovir dose of 800 mg orally twice daily is recommended (Nosari 2012).

Patients treated with alemtuzumab, an anti-CD52 monoclonal antibody, are prone to infections because of additive neutropenia and profound suppressive effects on the B, T, and natural killer cells. The defects with cellular immunity occur shortly after initiating alemtuzumab. This effect can last as long as 9 months after discontinuing alemtuzumab (Morrison 2009). This drug is associated with CMV reactivation, with an incidence of 4%–29% of patients with CLL (Morrison 2009; Faderl 2005). Onset of symptomatic CMV reaches its peak 4–6 weeks after initiating alemtuzumab (O'Brien 2006). Prophylaxis with valganciclovir 900 mg orally daily is the most effective treatment. Duration of prophylaxis is 2 months after the end of therapy and until the $CD4^+$ lymphocyte count is at least 200/mm^3. Cytomegalovirus reactivation should be monitored by PCR at baseline, every 2 weeks during treatment, and after therapy completion until prophylaxis is discontinued, especially in patients who are CMV seropositive at baseline. Despite negative baseline serology, fever of unknown origin should be tested for CMV reactivation. Onset is less likely after completing therapy. Screening of CMV antigen should also be by PCR every 2 weeks during prophylaxis (Morrison 2009; O'Brien 2005). Alemtuzumab also warrants

Table 1-8. Drug Class and Prophylaxis Indications

	Bacterial	HSV	CMV	PJP	Fungal	HBVR
Alkylating agents	No	No	No	No	No	No
Purine analogs (fludarabine, cladribine, pentostatin)	No	Yes	No	Yes	No	No
Anti-CD52 monoclonal antibody (alemtuzumab)	No[a]	Yes	Yes[b]	Yes	No[c]	Yes[d]
Anti-CD20 monoclonal antibodies (rituximab, obinutuzumab, ofatumumab)	No	No	No	No	No	Yes[d]
Phosphatidylinositol 3-kinase inhibitor (idelalisib)	No	No	No	Yes	No	No

[a]National Comprehensive Cancer Network suggests consideration of fluoroquinolone prophylaxis.

[b]Management is controversial. If viremia is present or rising, may use ganciclovir (orally or intravenously); CMV viremia should be monitored at least every 2–3 weeks by quantitative PCR.

[c]Give antifungal prophylaxis if alemtuzumab is given in combination with glucocorticoids.

[d]Give HBVR prophylaxis if patient is identified as high risk.

HBVR = hepatitis B virus reactivation; HSV = herpes simplex virus; PJP = *P. jiroveci* pneumonia.

Information from: Morrison V. UpToDate: Prevention of infections in patients with chronic lymphocytic leukemia [homepage on the Internet].

Pneumocystis prophylaxis. Sulfamethoxazole/trimethoprim 1 double-strength tablet orally three times weekly is recommended until at least 6 months after cessation of alemtuzumab treatment (Nosari 2012).

Anti-CD20 monoclonal antibodies and alkylating agents do not warrant antimicrobial prophylaxis. However, anti-CD20 monoclonal antibodies have been associated with risks of hepatitis B virus reactivation (HBVR) in high-risk patients. This is discussed in the next section.

As discussed earlier, patients receiving idelalisib should receive PJP prophylaxis and monitoring for CMV infection.

See Table 1-8 for a list of antibiotic prophylaxis recommendations per class of agent used in CLL treatment. Box 1-2 lists typical doses and schedules for the anti-infectives.

Hepatitis B Virus Reactivation

Assessment

Anti-CD20 monoclonal antibodies such as rituximab, ofatumumab, and obinutuzumab bind to CD20 and deplete B cells by antibody-dependent cellular cytotoxicity. Like many immunosuppressive therapies, these monoclonal antibodies are associated with a risk of HBVR. In 2013, the FDA added a boxed warning regarding the risk of HBVR to the labeling of monoclonal antibodies directed against CD20. This was also accompanied by the recommendation to screen for HBV before initiating the monoclonal antibody. Hepatitis B virus reactivation can ultimately lead to fulminant hepatitis, hepatic flares, liver failure, and even death (Perrillo 2015; FDA 2013). The most evidence of HBVR has been documented with rituximab use. Data on the other anti-CD20 antibodies are scarce; however, because of a similar mechanism of action and only a few cases, there is an assumption that all B cell–depleting drugs create a risk of HBVR (Perrillo 2015). Alemtuzumab, an anti-CD52 monoclonal antibody, has also

Box 1-2. Pathogens and Prophylactic Regimens

HSV

- Acyclovir 400–800 mg orally twice daily
- Valacyclovir 500 mg orally two or three times daily
- Famciclovir 250 mg orally twice daily

CMV

- Valganciclovir 900 mg orally once daily with food
- Ganciclovir 5 mg/kg intravenously once daily

PJP

- Trimethoprim/sulfamethoxazole 1 single-strength tablet orally once daily or 1 double-strength tablet orally once daily or three times weekly
- Dapsone 100 mg orally once daily
- Pentamidine 300 mg by aerosolized inhalation every 4 wk
- Dapsone 200 mg orally PLUS pyrimethamine 50–75 mg orally PLUS leucovorin 25 mg orally once weekly

CMV = cytomegalovirus; HSV = herpes simplex virus; PJP = *P. jiroveci* pneumonia.

Information from: National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology Prevention and Treatment of Cancer-Related Infections, version 2, 2016.

Table 1-9. Initial Tests for Assessing Risk of HBVR

Test and Description	Application
Hepatitis B surface antigen (HBsAg) • Protein on surface of virus ◦ HBV is present	Detects acute HBV infections • Even before symptoms occur • Not detectable during recovery period Detects chronic HBV infections • Identifies persistent HBV carrier
Hepatitis B core antibody (anti-HBc) • IgM and IgG antibodies to hepatitis B core antigen[a]	Detects acute or chronic HBV infections • IgM is first antibody produced after infection with HBV • IgG is produced later in course of infection and remains for life
(Optional) Hepatitis B surface antibody (anti-HBs) • Antibody to HBsAg	Detects previous HBV exposure • Successful vaccination or immune because of recovery from HBV infection • Long-term protection ◦ Possible HBV reactivation in immunosuppressed patients • Cannot pass virus to others

[a]For screening, require testing for IgG, not IgM.

HBV = hepatitis B virus.

Information from: American Association for Clinical Chemistry (AACC). Lab Tests Online. Hepatitis B Testing. 2016; Hwang JP, Somerfield MR, Alston-Johnson DR, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Clin Oncol 2015;33:2212-20; and Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170-80.

been identified as a high-risk agent for HBVR. The general consensus states that all patients receiving anti-CD20 monoclonal antibody therapy or alemtuzumab should initially be screened for risk of reactivation by obtaining hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) status before starting therapy (Zelenetz 2017; Perrillo 2015). The risk of HBVR occurring is associated with the combination of hepatitis B virus (HBV) serologic status, HBV DNA level, and immunosuppressive potential of the drug (Gonzalez 2016). In a retrospective analysis involving patients with positive HBsAg status treated with rituximab and chemotherapy, HBVR occurred in 28.6% of patients (Kim 2013). In this same population, 10.1% of patients with positive anti-HBc had HBVR (Kim 2013). Positive HBsAg identifies acute or chronic infection. Anti-HBc may depict acute or chronic infection through detection of antibodies. Immunoglobulin (Ig) M is produced immediately after HBV infection, whereas IgG is present later in the infection and remains for life. In certain circumstances, hepatitis B surface antibody (anti-HBs) may also be obtained to further evaluate risk. Positive anti-HBs generally depicts protective immunity either by vaccination or by natural infection. Ultimately, obtaining the HBV DNA level through a quantitative PCR determines a patient's viral load and is the best predictor of reactivation (Yeo 2004). Elevation in ALT, together with the DNA viral load, is also recommended when monitoring for HBVR.

If either HBsAg or anti-HBc is positive, a baseline viral load should be determined by obtaining the HBV DNA; a negative PCR does not eliminate the chance of HBV reactivation. Table 1-9 describes the initial tests used to screen for risk assessment. Table 1-10 describes the appropriate intervention according to HBsAg and anti-HBc results.

Management

Patients with HBsAg positivity or anti-HBc positivity should receive prophylactic antiviral therapy, regardless of viral load or presence of clinical manifestations of HBVR. Of note, patients with a history of hepatitis, or chronic liver disease, may have a false-negative HBsAg; if so, they should further be assessed by measuring DNA viral load. In addition, patients may be falsely anti-HBc positive if they are receiving intravenous immunoglobulin (Arnold 2010). In these same patients, the DNA viral load may be obtained to detect active disease. However, the viral load may still be undetectable, or it may naturally be low because the virus has most likely serologically cleared at this point (Evens 2011). Despite this, there is still a risk of reactivation with anti-CD20 or anti-CD52 monoclonal antibody therapy (Hwang 2015). Prophylactic antiviral therapy is preferably entecavir 0.5 mg orally once daily. Acceptable alternatives are adefovir, telbivudine, and tenofovir. Lamivudine is not recommended because of the risk of resistance (Zelenetz 2017). Hepatitis viral load with PCR should be

Table 1-10. Next Steps for HBV Panel Results

HBsAg[a]	Anti-HBc	Anti-HBs	Interpretation	Action
+	±	N/A	Acute or chronic HBV infection At risk of HBV reactivation Incidence 20%–50%	Start antiviral prophylaxis Monitor with HBV DNA and ALT concentrations Consult hepatologist/HBV specialist
–	+	+	Infection resolved, virus cleared, immunity because of natural infection At risk of HBV reactivation Incidence up to 10%	Start antiviral prophylaxis Monitor with HBV DNA and ALT concentrations Consult hepatologist/HBV specialist
–	+	–	Interpretation unclear Four possibilities • Resolved infection (most likely) • Low-level chronic infection • Resolving acute infection • False-positive anti-HBc[b]	Start antiviral prophylaxis Monitor with HBV DNA and ALT concentrations Consult hepatologist/HBV specialist If potentially false positive anti-HBc, investigate further[b]
–	–	+	Immunity because of vaccination Not at risk of reactivation except for immunosuppressed patients	Consult hepatologist/HBV specialist
+	–	N/A	Acute infection, usually with symptoms; contagious; or chronic infection flare	Start antiviral prophylaxis If high HBsAg concentrations, monitor HBV DNA, and if increasing viral load, preemptively treat with antiviral therapy

[a]False-negative HBsAg if patient has history of hepatitis, or chronic liver disease.

[b]False-positive anti-HBc if patient receiving immunoglobulin therapy.

N/A = not applicable.

Information from: Zelenetz AD, Gordon LI, Wierda WG, et al. National Comprehensive Cancer Network Guidelines, version 1, 2017. Chronic lymphocytic leukemia/small lymphocytic lymphoma; American Association for Clinical Chemistry (AACC). Lab Tests Online. Hepatitis B Testing. 2016; Hwang JP, Somerfield MR, Alston-Johnson DR, et al. Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Clin Oncol 2015;33:2212-20; Ikeda M. Reactivation of hepatitis B virus in patients receiving chemotherapy. Jpn J Clin Oncol 2013;43:8-16; and Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170-80.

monitored throughout treatment and every 3 months thereafter during prophylaxis. A meta-analysis showed that most HBVR cases associated with rituximab occurred within the first 3 months of discontinuing rituximab (Evens 2011). Furthermore, 29% of HBVR cases appeared greater than 6 months after discontinuation. Reactivation has occurred as late as 12 months after rituximab discontinuation; therefore, some recommendations are to continue monitoring and antiviral therapy for as long as 12 months (Perrillo 2015; Evens 2011). If there is evidence of HBVR during anti-CD20/anti-CD52 monoclonal antibody therapy, therapy should be discontinued, and a hepatologist or HBV specialist should be consulted.

Hypogammaglobulinemia

Humoral and cell-mediated immune defects are inherent to patients with CLL. With humoral immunity, hypogammaglobulinemia is the major defect. It occurs in 10%–100% of patients with CLL (Nosari 2012). At some point in CLL, patients will develop hypogammaglobulinemia. Cytokines that are released from the malignant B cells are thought to have inhibitory action on immunoglobulin synthesis, resulting in decreased production (Nosari 2012). Hypogammaglobulinemia is a predominant risk factor for infections in the patient with CLL. Higher incidence is related to later stages of CLL and longer disease duration. At 5 years, the rate of severe infections was 26% overall, but rates were 57% in patients with a low IgG and 68% in patients with both a low IgG concentration and Binet stage C disease (Nosari 2012). Even with responses to treatment, hypogammaglobulinemia is not restored or improved. In general, early-stage and treatment-naive patients with CLL often develop infections that are related to hypogammaglobulinemia and encapsulated bacteria. In advanced stages and newer treatments such as the purine analogs, the types of infections also include opportunistic organisms (Tsiodras 2000).

A strong correlation between a specific immunoglobulin class and infectious risk has not been shown; however, low serum IgG concentrations are associated with an increased number of infections (Nosari 2012; Morrison 2001; Molica 1994). Hypogammaglobulinemia especially involves subtypes IgG3 and IgG4. Low IgG concentrations are associated with *Streptococcus*- and *Haemophilus*-associated recurrent bacterial infections. The respiratory tract is the most common infection site. This may be related to serum IgG4 and IgA deficiencies and mucosal immune defects (Morrison 1996).

Replacement of immunoglobulins in patients with hypogammaglobulinemia is controversial. However, prophylaxis with immunoglobulins in patients with recurrent and severe infections and/or hypogammaglobulinemia has reduced the incidence and severity of infections (Griffiths 1989). One of the largest trials was a multicenter, randomized, double-blind study of 84 patients with CLL who had hypogammaglobulinemia and/or a history of infection (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia 1988). Immunoglobulin 400 mg/kg or placebo every 3 weeks was given for 1 year. Immunoglobulin administration resulted in significantly fewer infections in patients with minor or moderate bacterial infections. However, there was no significant reduction in major infections or mortality. Immunoglobulin can reasonably be administered in patients with recurrent infections requiring intravenous antibiotics or hospitalization and with serum IgG concentrations less than 500 mg/dL. The usual immunoglobulin dose is 200–400 mg/kg every 3–4 weeks. As a general guideline, the trough serum IgG concentration should be maintained at 500–700 mg/dL. The optimal subset of patients who would benefit from immunoglobulin prophylaxis remains undetermined.

Vaccinations should also be considered in the patient with CLL. For more information, see the chapter on vaccinations in the patient with immunocompromise.

Autoimmune Disorders

Autoimmune disorders have strongly been associated with lymphoproliferative diseases, especially in the CLL population. Three autoimmune hematologic conditions commonly occur with CLL: autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), and pure red cell aplasia (PRCA) (Diehl 1998).

Autoimmune Hemolytic Anemia

Incidence

Autoimmune hemolytic anemia is the most common autoimmune disorder associated with CLL. Autoimmune hemolytic anemia alone is not associated with poor prognosis (Gribben 2010). The incidence of AIHA increases with more advanced stages of CLL (Mauro 2000). For Binet stage A, the incidence of AIHA is 4%, whereas stages B and C have an incidence of 10%. The exact etiology of this autoimmune disorder in CLL is unclear. Risk factors for AIHA include radiation, alkylating agents, and purine analogs. These therapies may disrupt lymphocyte subsets, resulting in an autoimmune clone (Mauro 2000). However, this does not explain the one-third of patients who had autoimmune disorders concurrently with the malignant disease before any treatment was given (Duhsen 1987). Abnormal production of autoantibodies and T-cell dysfunction are thought to contribute to the pathogenesis of AIHA associated with CLL (Diehl 1998).

Purine analogs are associated with a higher incidence of AIHA. However, a purine analog like fludarabine has a lower incidence of AIHA when used in combination with cyclophosphamide and/or rituximab. Prevention of fludarabine-associated AIHA may be because of the temporary B-cell depletion induced by rituximab (Zecca 2001).

Diagnosis/Treatment

This autoimmune disorder is diagnosed when there is an isolated decrease in hemoglobin and a positive direct antiglobulin (Coombs) test, indirect hyperbilirubinemia, reticulocytosis, reduced haptoglobin, and elevated LDH. Not all laboratory abnormalities need to be met in any given patient with AIHA. Treatment of AIHA associated with CLL is similar to that of AIHA in other patients. One treatment option is prednisone 1 mg/kg/day orally for 2–4 weeks, followed by a slow taper. In severe cases, methylprednisolone 1 g intravenously as a single dose or immunoglobulin 0.4 mg/kg/day intravenously for 5 days may be considered, in which response occurs in 40% of patients with AIHA. If there is relapse during steroid withdrawal or a patient is steroid refractory, cyclosporine 5–8 mg/kg/day has been effective in more than 60% of patients with a median duration of 10 months. Mycophenolate mofetil, splenectomy, rituximab 375 mg/m^2/week for 4 weeks with or without corticosteroids, and alemtuzumab have all been used to treat AIHA (Gribben 2010; Zecca 2001).

Idiopathic Thrombocytopenic Purpura

Incidence

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by thrombocytopenia caused by destruction of platelets. It is considered a secondary ITP when associated with autoimmune dysfunction or the presence of a lymphoproliferative disorder such as CLL. The incidence of ITP in patients with CLL is 2%–5%. Idiopathic thrombocytopenic purpura can occur at any stage of CLL, with more advanced ITP presenting at later stages. Idiopathic thrombocytopenic purpura in CLL is not associated with a poor prognosis, nor does it imply disease progression (Kaden 1979). Autoimmune hemolytic anemia may occur concurrently with ITP in up to one-third of patients with CLL-related ITP. Autoantibodies with both AIHA and ITP cause an immune destruction of both RBCs and platelets. This combination is called the Evans syndrome (Evans 1951).

Diagnosis/Treatment

An unexplained, rapid decrease in platelets in the absence of bone marrow failure or hypersplenism may suggest a diagnosis of ITP. Bone marrow aspirate and biopsy reveal normal to increased bone marrow megakaryocytes. Idiopathic thrombocytopenic purpura associated with CLL has both abnormal autoantibody production and T-cell dysfunction.

Treatment of ITP in patients with CLL has only been established through a few case reports. Treatment is comparable with traditional ITP. Corticosteroids (e.g., prednisone 1 mg/kg/day orally) are first-line therapy. This is associated with a response rate of more than 50% (Gribben 2010). Corticosteroids may induce lymphocytosis. This increase should not be mistaken for disease progression. Lymphocytes usually return to baseline within months (Boggs 1966). This lymphocytosis is similar to the B-cell receptor treatments ibrutinib and idelalisib. Splenectomy is another treatment option. It should be considered in stable patients with symptomatic massive splenomegaly or patients with chronically progressive cytopenias. Other treatments include immunoglobulins, rituximab, and vincristine. Response to initial treatments is about 50%, and despite several treatments, 20% of patients have refractory disease (Dearden 2008).

Pure Red Blood Cell Aplasia

Incidence

Pure red blood cell aplasia is manifested as severe anemia, the disappearance of red cell precursors from the bone marrow, and a drastic decrease in absolute reticulocyte count. Incidence of PRCA is up to 6%, but it may be underreported because of the difficulty in identifying it (Diehl 1998). The pathophysiology of PRCA associated with CLL is thought to be caused by abnormal T cells inhibiting the growth of erythroid progenitor cells.

Onset is insidious. Pure red blood cell aplasia can occur in early-stage disease. Patients may not have signs or symptoms of anemia until it becomes severe. First symptoms may include extreme pallor and marked fatigue. Overall survival of patients with PRCA depends on the etiology. Pure red blood cell aplasia secondary to leukemia or lymphoma is associated with an OS of 4 years, whereas primary or idiopathic PRCA has an OS of over 10 years (Clark 1984).

Diagnosis/Treatment

Pure red blood cell aplasia is diagnosed through the manifestation of severe anemia, a drastic decrease in absolute reticulocyte count by peripheral blood smear, and an absence of hematopoietic precursors through bone marrow aspiration in patients with CLL. This severe anemia is a net result of complete, or almost complete, cessation of red cell production. The serum iron concentration increases when the bone marrow ceases red cell production and stops the transfer of iron from the plasma to the bone marrow. The level of total iron-binding capacity is also affected, including transferrin saturation increasing up to 100% and unsaturated iron binding capacity approaching zero. Other cell lineages, like platelets and neutrophils, appear normal (Diehl 1998; Chikkappa 1987). Differential diagnosis should include viral infections associated with PRCA and pancytopenia (e.g., CMV, Epstein-Barr virus, parvovirus).

Pure red blood cell aplasia has no standard treatment for initial or relapsed disease. Treatment of PRCA is very similar to treatment of AIHA. No prospective randomized trials compare transfusions with the various regimens used to treat PRCA or compare between these regimens. Treatment of PRCA can include control of CLL itself. Treatment of PRCA includes RBC transfusions, but it can also be active treatment. Response rates to these treatments are 30%–55%.

Red blood cell transfusion is a treatment option for severe and symptomatic anemia. Risks associated with transfusions in patients with CLL are similar to those in other patients. Patients with CLL and PRCA may require repeated episodes of transfusions. Washed red cells and, uncommonly, leukocyte-depleted red cells are considered in these patients. Blood products that are irradiated are used in severely immunosuppressed patients to decrease the risk of transfusion-related graft-vs.-host disease.

Corticosteroids may be first-line treatment for PRCA (Diehl 1998). The usual dose is prednisone 1 mg/kg/day, and responses occur at 3–20 weeks. If there is no response by 4 weeks, cyclosporine can be added. Reticulocyte counts should respond within 2–3 weeks. Hemoglobin should return to normal values within 1–2 months, and corticosteroids can begin to be tapered (Diehl 1998).

Complete treatment response with oral cyclosporine occurs in most patients with CLL and PRCA (Tura 1988; Chikkappa 1987). Overall response rates are 65%–87% in the literature (Sawada 2009). Cyclosporine is thought to inhibit T-cell production to decrease the activity of the abnormal T-cell population (Tura 1988). There is no consensus on the standard dose of oral cyclosporine. Doses in the literature are 200–600 mg/day (Sawada 2008). Dose adjustments were made according to serum trough concentrations, response, and tolerance. Consideration was also given for renal function, hepatic function, and serum magnesium and potassium concentrations. Adverse effects are not prominent, except for mild reversible renal toxicity. With cyclosporine, responses occur at 7–10 days, as shown by an increase in the reticulocyte count, with hemoglobin concentrations returning to normal within 30–60 days (Diehl 1998). After 5–7 months on cyclosporine, tapering may begin slowly.

Patients with refractory PRCA may respond to rituximab therapy at a dose of 375 mg/m^2 intravenously weekly for 8 weeks (Ghazal 2002). Replacement therapy with immunoglobulins may be warranted because B-lymphocyte recovery does not start until 6–9 months after completing rituximab. This reduction in immunoglobulins (IgM, IgG) poses a risk of infection (Ghazal 2002).

Second Malignancies–Richter Transformation

Description

Patients with CLL have a higher risk of acquiring secondary malignancies, both hematologic and solid. The more common cancers are the same as those in patients without CLL: breast, lung, colon, and prostate cancers. This may be because of the underlying disease, chronic immunosuppression, and/or the treatments. Furthermore, these solid tumors may have worse survival in patients with CLL than in patients without CLL, though the reason for inferior survival is unclear. More studies are needed to address whether a different treatment strategy is required for these patients. Hematologic cancers with increased frequency include Richter transformation (RT), myelodysplastic syndrome, acute myeloid leukemia, T-cell lymphoma, Hodgkin lymphoma, and prolymphocytic leukemia.

Richter transformation is the development of an aggressive, higher-grade non-Hodgkin lymphoma, usually diffuse large B-cell lymphoma, in patients with CLL. Incidence is 2%–9%, with increasing frequency on the basis of prior treatments. Median time from diagnosis of CLL to RT is 21.9 months (range 1–66 months) (Morrison 1999), and transformation is associated with an unfavorable prognosis. Onset of RT is usually preceded by a constellation of rapid increase in lymphadenopathy at one or more sites, development of systemic B symptoms (fever, weight loss, night sweats), and sudden clinical deterioration (Robertson 1993). Additional clinical features are listed in Table 1-11. Although these features are common in CLL, none is pathognomonic for RT. A positive biopsy is required to establish the diagnosis of RT. Biopsy should be done at the site of greatest transformation, usually an enlarging lymph node. Histologic confirmation is necessary to confirm a diagnosis of RT. Richter transformation may be managed with traditional non-Hodgkin lymphoma treatments, but response rates are lower than for primary non-Hodgkin lymphoma, and patients typically die within a few months after transformation (Tsimberidou 2006).

Table 1-11. Clinical Features Associated with RT

Clinical Feature	Associated with RT (%)
Elevated serum lactase dehydrogenase (at least 2 x upper limit of normal)	82
Progressive lymphadenopathy (usually abdominal because of splenomegaly, hepatomegaly, retroperitoneal adenopathy)	64
Systemic symptoms (fever, weight loss, night sweats)	59
Monoclonal gammopathy	44
Extranodal involvement (GI tract, CNS, skin, eye, testis, and lung or kidney)	41

RT = Richter transformation.

Information from: Robertson LE, Pugh W, O'Brien S, et al. Richter's syndrome: a report on 39 patients. J Clin Oncol 1993;11:1985; and Tsimberidou AM, Keating MJ. Richter syndrome: biology, incidence, and therapeutic strategies. Cancer 2005;103:216-28.

Chemotherapy regimens used to treat RT are the same as those that are effective in high-grade non-Hodgkin lymphoma or acute lymphoblastic leukemia. Drugs within these various regimens are usually non–cross-resistant and have no overlapping adverse effects. One regimen, hyper-CVXD (fractionated cyclophosphamide, vincristine, liposomal daunorubicin, and dexamethasone), resulted in an ORR of 41% (complete response 38%) with a median OS of 10 months (Dabaja 2001). Overall response rates with these regimens were 5%–40%. Adding rituximab to combination chemotherapy improved the ORR to 41% (CR 18%). Median survival was also 10 months (Tsimberidou 2003). Thus, adding rituximab offered no additional benefit. Richter transformation usually presents as a disseminated disease at the time of diagnosis. Radiation therapy is used for palliation to control local pain and symptoms associated with bulky lymphadenopathy or extranodal disease (Tsimberidou 2005).

Autologous and allogeneic hematopoietic cell transplants are therapeutic options, given the poor efficacy of combination chemotherapy, short duration of remission, and poor OS of patients with RT. In patients in remission after chemotherapy or chemoimmunotherapy, those who received allogeneic stem cell transplants had longer survival than patients who received no additional treatment or autologous/allogeneic stem cell transplantation as salvage therapy (Tsimberidou 2006). In another study, three of eight patients who received allogeneic stem cell transplants compared with conventional chemotherapy had durable remission. These patients continued to be free of disease at 14 months, 47 months, and 67 months (Rodriguez 2000). Benefit appears to be greater in patients with chemosensitive disease. Autologous hematopoietic cell transplantation, as opposed to allogeneic, may be preferred in older adults and/or those with chemosensitive disease.

Richter transformation should be considered in patients with CLL who develop rapidly progressive lymphadenopathy or extranodal sites of disease, systemic symptoms, or elevated serum lactate dehydrogenase. Unfortunately, less aggressive and more curative treatment strategies are needed.

Psychosocial Effects

Because of CLL's indolent course, it poses some unique psychosocial needs. Establishing a relationship of open communication with patients is important. Identifying a caregiver as an additional point of contact should also be established.

Patients with newly diagnosed CLL should be provided education about their disease at the time of test result confirmation. It is important to review the results with patients to help them understand how disease biology is used to personalize treatment. Depending on the symptoms, blood count, and need for treatment, some patients may be seen at 3-month intervals or longer.

Education, open communication, and psychological support are key to provide to patients with CLL. Included in the education should be a clear understanding that CLL can become aggressive, so patients must be diligent about making appointments, despite feeling well. Patients should be assured that emerging therapies are improving the treatment of CLL. Medication education from the pharmacist is essential. Key discussion points may include drug interactions, safe use of OTC and herbal supplements, and potential adverse effects with their treatments. Patients should also be provided open communication between them and the health care team. They should be able to readily contact the provider and staff for anything, no matter how trivial it may seem. It should be stressed that concerns that seem unimportant may progress to serious situations. Psychological support should also be addressed. Patients with CLL should be assessed for distress and anxiety. Of interest, active surveillance, or the decision to "watch and wait," had a health-related quality of life (HRQoL) equal to that in the normal population (van den Broek 2015). This is in opposition to the treated patients who had significantly poorer HRQoL than the normal population. This may be because of worse disease and adverse effects of the treatment itself. However, anxiety and depressive symptoms did not differ between the treated patients and those under active surveillance (van den Broek 2015). Therefore, it is vital that all patients receive adequate emotional support. To ensure understanding, it is important to provide written material and reiterate important points. It may also be helpful to provide professional websites and other reputable resources such as the American Cancer Society and the Leukemia & Lymphoma Society.

Another aspect of treating patients with CLL is the element of cost. Newer agents like ibrutinib, idelalisib, and venetoclax have undoubtedly improved the treatment with respect to survival while providing a convenient dosage formulation, but they also have a heavy price tag. An analysis of the pharmaceutical cost impact of ibrutinib and idelalisib found that, per patient, the current annual price of these agents is about $118,000 per year, which is more than twice the average annual U.S. household income (Shanafelt 2015). Societal cost of the approval of ibrutinib and idelalisib in previously treated patients increased by up to 70%. These oral agents are covered by Medicare Part D, which becomes a significant increase in out-of-pocket expense compared with the parenteral treatment that is covered by Medicare Part B. This can potentially hinder access and adherence to these drugs. Some may say that the benefit of these newer agents is overshadowed by the financial burden, limited access, and potential adherence issues that accompany them. Pharmacists can play a role in referring patients to assistance programs to help alleviate the financial burden these medications can create.

Practice Points

- **Molecular cytogenetics occurs in most patients with CLL during the disease.**
  - **These chromosomal abnormalities are associated with a degree of prognoses.**
  - **Currently, only del(17p) plays a direct role in treatment selection.**
- **Ibrutinib has uncommon but serious adverse effects such as bleeding tendencies and atrial fibrillation and flutter.**
- **Idelalisib has significant adverse effects of liver enzyme elevation and diarrhea. Both can be managed when adequately identified.**
- **Ibrutinib, idelalisib, and venetoclax are associated with significant drug-drug interactions with CYP3A inhibitors and inducers that may warrant dose modification.**
- **Ibrutinib and idelalisib are B-cell receptor antagonists that are associated with lymphocytosis, which**
  - **does not represent disease progression unless accompanied by other signs of disease progression**
  - **has a peak effect at 2 weeks and duration of about 8–12 months**
- **Antimicrobial prophylaxis is currently warranted in the medications used to treat patients with CLL (purine analogs [fludarabine, cladribine, pentostatin], alemtuzumab, and idelalisib) as well as in patients at high risk of HBVR.**
- **Anti-CD20 and anti-CD52 monoclonal antibodies have been associated with a high risk of HBVR. Patients receiving these drugs should be screened to identify whether they are at high risk and require antiviral prophylaxis.**
  - **False-positive HBc can occur in patients receiving intravenous immunoglobulin.**
- **Hypogammaglobulinemia should be treated with intravenous immunoglobulin when patients have had recurrent infections requiring hospitalizations or intravenous antibiotics and serum IgG concentrations less than 500 mg/dL.**
- **Evans syndrome occurs when AIHA and ITP are both present in the patient with CLL.**
  - **Occurs in one-third of patients with ITP**
  - **Common treatments for AIHA and ITP include corticosteroids, intravenous immunoglobulins, splenectomy, and rituximab.**
- **Pure red cell aplasia has no standard treatment. It is treated similarly to AIHA.**
- **Richter transformation may be preceded by a rapid increase in lymphadenopathy, B symptoms, and sudden clinical deterioration. A positive biopsy is required for diagnosis.**

CONCLUSION

Patients with CLL have a broad spectrum of potential outcomes. In some, the indolent course of CLL presents unique psychosocial needs and a required understanding by patients

of their disease. For those needing treatment, several newer drugs have provided convenient therapies and different mechanisms of actions. Some of these agents have improved specificity and a more tolerable adverse effect profile. These agents give more options for a disease state that afflicts an older and frailer population. With the various pharmacologic functions, optimal combinations and sequences of these newer agents are not yet known.

Despite adequate therapeutic interventions, a variety of complications and comorbidities occur with CLL. These include infections, autoimmune disorders, and secondary malignancies. Managing these complications while treating the lymphoproliferative disease itself can be challenging.

As more agents are discovered and developed, pharmacists will be relied on as the medication experts. Roles will include ensuring appropriate dosing, recognizing and managing the adverse effects, and identifying drug interactions. The future looks brighter for the treatment of CLL as we add to our armamentarium of therapies.

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Self-Assessment Questions

1. A 42-year-old woman with a diagnosis of chronic lymphocytic leukemia (CLL) is treated by "watch and wait." Which one of the following signs/symptoms would most indicate progressive disease, thus warranting active treatment for this patient?

   A. Progressively decreasing IgG concentrations
   B. Cytogenetic demonstration of del(11q)
   C. Elevated serum lactate dehydrogenase
   D. Progressive splenomegaly (over 6 cm below left costal margin)

2. A patient with newly diagnosed CLL has no cytogenetic abnormalities. The patient is treated with ibrutinib. After 10 months of treatment with ibrutinib, the CLL relapses. Which one of the following is the best next step for this patient?

   A. Continue ibrutinib at a higher dose.
   B. Recheck for cytogenetic abnormalities.
   C. Start venetoclax at the standard dose.
   D. Enroll patient in an investigational study.

3. The following table describes outcomes data from a recent study of patients with CLL:

   Patients with Indolent, Untreated, Benet Stage A CLL

	Chlorambucil + Prednisone (n=460)	No Treatment (n=466)	p value
Deaths	121 (47 related to CLL)	126 (65 related to CLL)	0.46
5-yr survival	81%	81%	NS
7-yr survival	71%	69%	0.77
Progression to stage B[a]	41	85	0.05
Progression to stage C[a]	17	26	0.04

NS = not significant.
[a]Stage at the time of the change in treatment.
Which one of the following best summarizes the results of this study?

   A. Treating at stage A prevents progression to stage B/C and improves survival.
   B. Treating at stage A does not prevent progression to stage B/C and does not improve survival.
   C. Waiting to treat until disease progresses to stage B/C affects survival.
   D. Waiting to treat until disease progresses to stage B/C does not affect survival.

4. A 65-year-old man with CLL and del(17p) has relapsed after treatment with fludarabine/cyclophosphamide/rituximab. His home drugs include acyclovir, trimethoprim/sulfamethoxazole, ranitidine, warfarin, and a multivitamin. Which one of the following is best to recommend for this patient?

   A. Ibrutinib
   B. Idelalisib
   C. Venetoclax
   D. Duvelisib

5. A 75-year-old man with relapsed CLL is treated with ibrutinib 420 mg orally daily. He recently fell and needs a hip replacement. Which one of the following is best to recommend regarding this patient's ibrutinib regimen?

   A. Lower the dose during the surgery.
   B. Hold for 3 days before and 3 days after surgery.
   C. Hold for 7 days before and 7 days after surgery.
   D. Discontinue permanently.

Questions 6 and 7 pertain to the following case.

Q.T. is a 68-year-old woman with relapsed CLL. She is treated with idelalisib 150 mg orally twice daily plus rituximab for 2 months. Her liver function tests have been monitored every 2 weeks. Q.T.'s ALT and AST concentrations have noticeably increased to 4 times the upper limit of normal.

6. Which one of the following is best to recommend for Q.T.?

   A. Continue current dose and monitoring of liver function tests every 2 weeks.
   B. Continue current dose and increase monitoring of liver function tests to every week.
   C. Decrease idelalisib dose to 100 mg orally twice daily and continue current monitoring plan.
   D. Discontinue idelalisib permanently.

7. Q.T. has now been treated with idelalisib plus rituximab for a total of 5 months. Her ALT and AST have decreased to 2 times the upper limit of normal. Which one of the following actions is best to recommend for Q.T. next?

   A. Monitor liver function tests at same frequency.
   B. Discontinue monitoring of liver function tests.
   C. Give idelalisib at a lower dose.
   D. Discontinue idelalisib permanently.

8. A 72-year-old woman with relapsed CLL has been treated with idelalisib 150 mg orally twice daily for the past 5 months and is doing well. Today, she presents to the clinic with complaints of loose, watery stools that began last week and are worsening (now 5 or 6 stools per day). She has tried loperamide, but it did not control

the diarrhea. Which one of the following is best to recommend for this patient?

A. Continue idelalisib and initiate budesonide 9 mg orally daily.
B. Discontinue idelalisib and initiate budesonide 9 mg orally daily.
C. Continue idelalisib and initiate prednisone equivalent 1 mg/kg/day intravenously.
D. No treatment should be initiated because the diarrhea is transient.

9. A 73-year-old man with high-risk CLL has received treatment with ibrutinib for 2 weeks. Last week, his lymphocyte count was 3000/mm^3; today in the clinic, it was 7000/mm^3. Which one of the following is best to recommend for this patient?

A. Permanently discontinue ibrutinib immediately.
B. Monitor for signs and symptoms of disease progression.
C. Hold ibrutinib until lymphocyte count decreases to baseline.
D. Increase ibrutinib dose by an increment of 140 mg.

10. A patient with CLL taking venetoclax has new-onset atrial fibrillation. The patient is subsequently initiated on amiodarone. Which one of the following is best to recommend for this patient?

A. Decrease amiodarone dose by 50%.
B. Increase amiodarone dose by 50%.
C. Decrease venetoclax dose by 50%.
D. Increase venetoclax dose by 50%.

11. A patient with CLL presents to your clinic. He is receiving treatment with alemtuzumab. His cytomegalovirus (CMV) PCR is negative, and he has no known allergies. Which one of the following is the best prophylactic anti-infective therapy for this patient?

A. Valganciclovir 900 mg orally daily; trimethoprim/sulfamethoxazole 1 double-strength tablet orally three times weekly
B. Acyclovir 800 mg orally three times daily; trimethoprim/sulfamethoxazole 1 double-strength tablet orally three times daily
C. Fluconazole 200 mg orally daily; trimethoprim/sulfamethoxazole 1 double-strength tablet orally three times weekly
D. Fluconazole 800 mg orally daily; trimethoprim/sulfamethoxazole 1 double-strength tablet orally three times daily

12. A frail 77-year-old woman with CLL presents at your clinic. She has no del(11q) or del(17p) mutations. She is currently treated with obinutuzumab plus chlorambucil. She has no known allergies. Which one of the following is best to recommend as anti-infective prophylaxis for this patient?

A. Acyclovir 400 mg orally twice daily
B. Fluconazole 200 mg orally daily
C. Trimethoprim/sulfamethoxazole double-strength 1 tablet orally once daily three times weekly
D. No prophylactic anti-infectives

13. A 69-year-old woman has a diagnosis of CLL and del(17p). She has been receiving alemtuzumab plus rituximab for 1 month. She was CMV seropositive at baseline. Two days ago, she came to the clinic with a temperature of 102°C. Her WBC is within normal limits. Cultures are negative and there appears to be no source of infection. The patient currently receives acyclovir 400 mg orally twice daily and trimethoprim/sulfamethoxazole 1 double-strength tablet orally every Monday, Wednesday, and Friday. Which one of the following is best to recommend for this patient?

A. Empirically start treatment with cefepime at appropriate doses.
B. Start prophylactic doses of fluconazole.
C. Stop trimethoprim/sulfamethoxazole and start dapsone 100 mg orally daily.
D. Obtain PCR for CMV DNA to detect reactivation of CMV.

14. Before receiving ofatumumab, a patient with CLL had the following hepatitis B virus (HBV) laboratory results: HBsAg negative, anti-HBc positive. Which one of the following options best describes these results?

A. Immunity because of immunization
B. Never infected and no evidence of immunization
C. Chronic or acute infection
D. HBV present

15. A patient is hepatitis B surface antigen (HBsAg) negative and hepatitis B core antibody (anti-HBc) positive. Which one of the following is best to recommend for this patient?

A. Start entecavir 0.5 mg orally once daily and continue for 12 months.
B. Start entecavir 0.5 mg orally once daily and continue for 3 months.
C. Do not start antiviral prophylaxis therapy and monitor with HBV DNA and ALT concentrations.
D. Do not start antiviral prophylaxis therapy and do not monitor with HBV DNA.

16. A patient with CLL is going to start rituximab. The patient is receiving intravenous immunoglobulin (IVIG) therapy for hypogammaglobulinemia. A hepatitis panel shows HBsAg negative and anti-HBc positive. Because of the potential false positive anti-HBc with IVIG use, a HBV

DNA level was obtained, which resulted as undetectable. Which one of the following is best to recommend for this patient?

A. Start antiviral prophylaxis therapy.
B. Do not start antiviral prophylaxis therapy.
C. Obtain anti-HBs.
D. Obtain another HBV DNA level in 1 week.

17. A patient with CLL is seen in the clinic with complaints of excessive sweating overnight and intermittent fevers. He presents with the following laboratory values: Hgb 12 g/dL, Plt 300,000/mm^3, absolute reticulocyte count 2%, neutrophils 70%, and LDH 1200 IU/L. Bacterial and viral cultures are negative. The patient's IgG is 900 mg/dL, and splenomegaly is present. Which one of the following best explains this patient's signs and symptoms?

A. Autoimmune hemolytic anemia (AIHA)
B. Richter syndrome
C. Pure red cell aplasia (PRCA)
D. Hypogammaglobulinemia

18. A patient with CLL appears in the clinic with the following laboratory values: Hgb 7.5 g/dL, Plt 100,000/mm^3, absolute reticulocyte count 3.5%, neutrophils 7%, and LDH 1000 IU/L. Bacterial and viral cultures are negative; IgG is 900 mg/dL; and a Coombs test is positive. The patient has no splenomegaly or hepatomegaly. Which one of the following best justifies a diagnosis of AIHA in this patient?

A. Low hemoglobin and decreased reticulocyte count
B. Low IgG concentrations and elevated LDH
C. Low platelet count and elevated LDH
D. Low hemoglobin and positive Coombs test

19. A patient with CLL is seen in the clinic with the following laboratory values: Hgb 7.5 g/dL, Plt 300,000/mm^3, absolute reticulocyte count 0.1%, neutrophils 70%, and LDH 200 IU/L. Bacterial and viral cultures are negative; no splenomegaly or hepatomegaly is present. Which one of the following best explains this patient's signs and symptoms?

A. PRCA
B. Richter transformation
C. Hypogammaglobulinemia
D. AIHA

20. A 65-year-old woman has CLL Rai stage III. Her second-line treatment has failed, and she is admitted to the hospital for the third time in 3 months for a bacterial infection. IgG level was 100 mg/dL. Which pair of patient characteristics best justifies the use of immunoglobulin in this patient for prophylaxis against infections?

A. Late stage CLL and no response to treatment for CLL
B. No response to treatment for CLL and IgG level
C. Repeated severe bacterial infections and late stage CLL
D. Repeated severe bacterial infections and IgG level

Learner Chapter Evaluation: Chronic Lymphocytic Leukemia.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Devise appropriate chronic lymphocytic leukemia (CLL) treatments on the basis of patient characteristics.
13. Develop management plans for adverse effects and drug interactions of drug therapy for CLL.
14. Design an antimicrobial prophylaxis regimen based on the drug therapy used for CLL.
15. Construct an appropriate management plan for hepatitis B reactivation with CLL drug therapy.
16. Detect or manage complications commonly experienced by patients with CLL.
17. Please provide any specific comments related to any perceptions of bias, promotion, or advertisement of commercial products.
18. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

Multiple Myeloma

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LEARNING OBJECTIVES

1. Demonstrate knowledge of the pathogenesis and risk factors for multiple myeloma (MM) as well as the clinical presentation of the disease.
2. Distinguish the different staging systems and the response criteria used in MM.
3. Evaluate patients with myeloma and design the appropriate treatment options, including new therapies.
4. Justify supportive care for issues including bone disease, thromboembolism, neuropathy, and prevention of infection associated with myeloma disease and treatment.

ABBREVIATIONS IN THIS CHAPTER

ASCT	Autologous stem cell transplantation
BM	Bone marrow
CR	Complete response
EFS	Event-free survival
FLC	Free light chain
HDT	High-dose chemotherapy
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PI	Proteasome inhibitor
PN	Peripheral neuropathy
PR	Partial response
R/R	Relapsed/refractory
SMM	Smoldering multiple myeloma
SRE	Skeletal-related event
VGPR	Very good partial response
VTE	Venous thromboembolism

Table of other common abbreviations.

INTRODUCTION

Multiple myeloma (MM) is a disorder of terminally differentiated plasma cells in the bone marrow (BM), producing a monoclonal immunoglobulin that crowds out normal-functioning immunoglobulins. The plasma cells that accumulate in the BM can lead to BM destruction, marrow failure, and osteolytic lesions that can lead to pathologic fractures.

The disease accounts for about 10% of hematologic malignancies and is the second most common hematologic malignancy in the United States. The American Cancer Society estimates that 30,330 new cases will be diagnosed in the United States in 2016, leading to 12,650 deaths. The mean age of diagnosis is 62 years for men (75% in older than 70 years) and 61 years for women (79% in those older than 70 years). The 5-year survival rate reported in the Surveillance, Epidemiology, and End Results Program databases increased from 25% in 1975 to 48.5% in 2012 because of the newer and more effective treatment options available (Dimopoulos 2016b; Siegel 2016).

Significant progress in understanding the pathogenesis of MM has been made in the past several years. Two key players in the pathogenesis of MM, which is characterized by dissemination of several tumor cells throughout the BM, have been identified: (1) genetic lesions intrinsic to the malignant clone; and (2) the interaction between myelomatous plasma cells and their microenvironment. Most patients with MM have cytogenetic abnormalities, and cytogenetics has become one of the most important prognostic factors. Common mutations include loss at 17p and inactivation of the tumor suppressor p53, resulting in immunoglobulin overproduction. Somatic mutations associated with MM development can be characterized as either non-hyperdiploid disease or hyperdiploid disease (HD). Non-hyperdiploid disease is characterized by chromosomal translocations at 14q32, including t(4;14), t(14;16), and t(14;20),

which involve early translocation of immunoglobulin heavy chain (IgH) genes. Non-hyperdiploid disease is linked with an increased likelihood of disease progression and poor overall prognosis. By contrast, HD is characterized by the presence of trisomies, specifically of one or more at chromosomes 3, 5, 7, 9, 11, 15, 19, and 21. Excess cyclin D in the absence of elevated IgH is the main signature of HD.

The second concept in MM pathogenesis consists of the interaction between the malignant clone and the stromal cells, which promotes tumor progression and drug resistance. The BM microenvironment (BMM) also includes T, natural killer, and dendritic cells, which play a critical role in immune surveillance. In addition to providing an optimal substrate for MM initiation and progression, the BMM can provide activated inflammatory substances, including cytokines, chemokines, adipokines (e.g., adiponectin and leptin), and growth factors (e.g., interleukin-6 [IL-6], insulin-like growth factor-1, vascular endothelial growth factor, tumor necrosis factor-alpha [TNFα], and stromal cell–derived factor-1) secreted by macrophages, neutrophils, and other cells in the BM, which support malignant cell growth, drug resistance, and cytotoxicity of healthy cells (Bianchi 2015; Rajan 2015).

Multiple myeloma is classified as either smoldering multiple myeloma (SSM) or active disease. A premalignant condition for MM is known as monoclonal gammopathy of undetermined significance (MGUS). Both MGUS and SMM are asymptomatic conditions requiring observation for signs of disease progression. Monoclonal gammopathy of undetermined significance is a relatively common condition present in about 3% of white patients older than 50. Monoclonal gammopathy of undetermined significance precedes MM development, with a lifelong rate of malignant transformation of 1% per year. Because of the slow rate of conversion, these patients are usually followed closely and do not need treatment. The risk of progression to malignancy in the first 5 years after diagnosis is 10% per year in SMM and 1% per year in MGUS. The standard of care for SMM is also observation until development of symptomatic MM. Smoldering multiple myeloma includes a high-risk subgroup of patients (discussed later in the text) with about a 50% risk of progression within 2 years, and these patients need to be considered for clinical trials testing early therapy (Rajkumar 2015; Kyle 2006).

Several risk factors are thought to increase MM development. Reports of MM occurring in the same family suggest a possible genetic component in disease development. Studies have reported that first-degree relatives of patients with MGUS or MM are 2–3 times more likely to develop MGUS or MM than are those without a family medical history. Other risk factors associated with MM include ionizing radiation and agricultural and occupational exposures, including organic solvents and pesticides. Race is also a risk factor, with African Americans at twice the risk as whites of developing MM. Finally, age is a predominant risk factor for developing MM or MGUS (Rajkumar 2016).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology of multiple myeloma (MM)
- The staging and diagnosis of MM
- Drug knowledge of the agents used to treat newly diagnosed MM
- Drug knowledge of the agents used to treat relapsed/refractory MM
- Drug knowledge of the agents used for maintenance of MM
- The complications of MM and the supportive care

Table of common laboratory reference values.

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- NCCN. (2016). National Comprehensive Cancer Network clinical practice guidelines in oncology for multiple myeloma v3. 2016.
- Rajkumar SV. Multiple myeloma: 2016 update on diagnosis, risk-stratification, and management. Am J Hematol 2016;91:719-34.

CLINICAL PRESENTATION

The main symptoms of MM are caused by the complications of MM that can be remembered using the CRAB acronym (hypercalcemia, renal dysfunction, anemia, and lytic bone lesions). These MM complications are the result of the infiltration of plasma cells into the bone or other organs. Infection is another complication that patients can have because of the immune dysfunction caused by the monoclonal protein. Some patients with MM may have no symptoms, and their disease can be diagnosed at an asymptomatic stage. These patients will only have laboratory abnormalities at presentation (Rajkumar 2014; Kyle 2003).

Hypercalcemia, caused by bone loss from tumor progression, is present in 28% of patients with a diagnosis of MM. Hypercalcemia can lead to renal dysfunction by causing volume depletion and dehydration. The mainstay of therapy for hypercalcemia is hydration, corticosteroids, and bisphosphonates (Kyle 2003).

Renal insufficiency is present in about 20% of patients with a diagnosis of MM. Kidney failure is partly caused by the filtration of excess light chains from the overproduction of the monoclonal immunoglobulin damaging the renal tubules. Another cause for increased creatinine is hypercalcemia. Acute renal failure as the result of cast nephropathy

is diagnosed if the circulating free light chain (FLC) concentrations are high (greater than 1500 mg/L). However, a renal biopsy is required if serum FLC concentrations are below 500 mg/L and cast nephropathy is suspected. Patients presenting with acute renal failure caused by light chain cast nephropathy need urgent treatment to lower circulating FLC concentrations. Acute renal failure as the result of MM can be reversible if treated early. Urgent treatment includes using plasmapheresis and initiating chemotherapy to treat the underlying condition (Hutchison 2012; Kyle 2003).

Anemia occurs in about 75% of patients and contributes to fatigue, weakness, and shortness of breath. It can be related to the crowding of plasma cells in the BM, leading to loss of RBC precursors, or kidney damage (Kyle 2003).

Bone lesions are defined as one or more osteolytic lesions on skeletal radiography, CT, or positron emission tomography-CT (PET-CT). Osteolytic skeletal lesions can be detected in about 80% of patients. Thirty percent of patients present with pathological fractures, and 60% present with acute back or chest pain. The mechanism of the lytic lesions are MM cells that increase osteoclast function and decrease osteoblast function, resulting in hypercalcemia, bone pain and fractures, or spinal cord compression. The most important element in supportive care is the use of bisphosphonates or radiation to prevent or reduce the number of skeletal lesions (Rajkumar 2014).

Patients with MM are also at risk of infection because of immune dysfunction caused by impaired lymphocyte function, suppression of normal plasma cell function, and hypogammaglobulinemia. Patients may benefit from intravenous immunoglobulin infusions if they are having consecutive infections within a short period (Kyle 2003).

DIAGNOSIS AND STAGING

Patients with suspected MM should have an initial diagnostic workup, including a medical history and physical examination. The diagnosis of MM may be suspected if one or more of the following are present: bone pain with osteolytic lesions on skeletal films, increased total protein and/or presence of monoclonal protein in urine or serum, unexplained anemia, hypercalcemia, or acute renal failure.

Baseline laboratory studies should be done for patients thought to have MM. These include blood tests for CBC with differential, renal function tests, LDH, and β_2 microglobulin (B2M) (Box 2-1). The B2M test reflects the tumor mass and is considered a standard measure of tumor burden. Serum analysis also includes quantitative immunoglobulin concentrations of different types of antibodies (immunoglobulin [Ig] G [IgG], IgA, and IgM) to specify the type of abnormal antibodies present. Urine tests are done to check for monoclonal protein (Bence Jones protein) in the urine. The BM biopsy and aspirate are evaluated to detect chromosomal abnormalities by cytogenetics and fluorescence in situ hybridization (FISH).

Box 2-1. Diagnostic Workup for Multiple Myeloma

Blood
- Serum protein electrophoresis and immunofixation
- Quantitative serum immunoglobulins
- Serum free light chain assay
- Total serum protein, serum albumin, LDH, β_2-microglobulin
- SCr, BUN, calcium, electrolytes
- Hgb, WBC, differential count, Plt

Urine
- Urine protein electrophoresis and immunofixation
- 24-hr urine for total protein, light chains

Bone Marrow
- Unilateral bone marrow aspirate and biopsy for plasma cell count, morphology
- Cytogenetic evaluation and fluorescence in situ hybridization for the detection of del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q+

Bones
- Skeletal survey (conventional radiography)

Specific chromosomal abnormalities have been identified in MM that have prognostic effects (Table 2-1). Gene expression profiling is a genomic tool that helps the clinician further understand the molecular subtypes of MM (Rajkumar 2014). It has the potential to provide additional prognostic value to further refine risk stratification, help in making therapeutic decisions, and inform novel drug design and development. Gene expression profiling is not currently routinely used in clinical practice during diagnostic workup, but it is

Table 2-1. Summary of Cytogenetic Risk Features

	High Risk	Standard Risk
Cytogenetic abnormality	FISH • Deletion 17p • Translocation (4;14) • Translocation (14;16) • Translocation (14;20) • Gain (1q) Non-hyperdiploid karyotype Karyotype del(13) GEP. High-risk signature	Translocation (11;14) Translocation (6;14)
Median OS (months)	24.5	50.5

FISH = fluorescence in situ hybridization; GEP = gene expression profiling; OS = overall survival.

Information from: Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015;33:2863-9.

a useful tool and may be helpful in selected patients to estimate disease aggressiveness and individualize treatment. A skeletal survey is indicated to assess for lytic bone lesions. The National Comprehensive Cancer Network (NCCN) also recommends additional tests like MRI, CT, or PET/CT scans when plain radiographs do not identify an abnormality for symptomatic areas (NCCN 2016).

According to the results of clinical and laboratory evaluations, patients are classified as having MGUS, SMM, or symptomatic MM (active MM) (Box 2-2). The NCCN guidelines recommend that patients with SMM be seen every 3–6 months or strongly recommend enrolling eligible patients in clinical trials. Patients with high-risk SMM, including those with specific cytogenetic abnormalities – especially t(4;14), 1q gain, and deletion 17p, have an estimated 50% risk of progressing to MM within 2 years.

Patients with active MM are staged according to either the Durie-Salmon staging system (DSS) or the Revised International Staging System (R-ISS) (Table 2-2). Compared with the DSS, the R-ISS is easier to compute, provides a better distribution of patients among the three disease stages, and is more commonly used in recent studies. The R-ISS is based on laboratory measurement and disease biology, such as presence of cytogenetic abnormalities or elevated LDH, to create a unified prognostic index. The 5-year survival rates are 82%, 62%, and 40% for R-ISS stage I, II, and III, respectively. A 2015 study showed that the R-ISS staging system is a new risk stratification algorithm with improved prognostic power compared with individual ISS, chromosomal abnormalities, and LDH parameters. In this study, about 26% of patients would have been incorrectly assigned to a good-prognosis group had only one of these three factors been considered to classify patients (Palumbo 2015).

Box 2-2. Revised IMWG Criteria for Diagnosis of MGUS, Asymptomatic and Symptomatic Myeloma

MGUS

- Monoclonal protein in serum < 3 g/dL
- BM clonal plasma cells < 10%
- No related organ or tissue impairment (no end-organ damage, including bone lesions)

SMM (Asymptomatic)

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL or urinary monoclonal protein ≥ 500 mg/24 hr and/or clonal BM plasma cells 10%–60% and
- Absence of myeloma-defining events or amyloidosis

Active (Symptomatic) Myeloma

Clonal BM plasma cells ≥ 10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

- Related organ or tissue impairment:
  - Hypercalcemia: Serum calcium > 1 mg/dL higher than the upper limit of normal or > 11 mg/dL
  - Renal insufficiency: CrCl < 40 mL/min/1.73 m^2 or SCr > 2 mg/dL
  - Anemia: Hgb > 2 g/dL below the lower limit of normal or Hgb < 10 g/dL
  - Bone lesions: ≥ 1 osteolytic lesions on skeletal radiography, CT, or PET-CT, whole-body MRI
- Any one or more of the following biomarkers of malignancy:
  - Clonal BM plasma cell percentage ≥ 60%
  - Involved/uninvolved serum FLC ratio ≥ 100
  - > 1 focal lesion on MRI studies

BM = bone marrow; FLC = free light chain; IMWG = International Myeloma Working Group; MGUS = monoclonal gammopathy of undetermined significance; SMM = smoldering multiple myeloma.

RESPONSE CRITERIA

A uniform classification by the International Myeloma Working Group (IMWG) was recently developed to assess treatment response in MM. The updated IMWG response criteria include definitions for complete response (CR), stringent CR, immunophenotypic CR, molecular CR, very good partial response (VGPR), partial response (PR), minimal response, stable disease, and progressive disease (Table 2-3 and Table 2-4).

TREATMENT OVERVIEW

Although MM remains incurable, overall survival (OS) in MM has improved significantly in the past 15 years with the emergence of thalidomide, bortezomib, and lenalidomide in addition to autologous stem cell transplantation (ASCT) in eligible patients. More recently, carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab were FDA approved for the treatment of relapsed MM, and these agents promise to improve outcomes further. Despite newer therapies, the goal of therapy continues to be prevention of disease progression and prolongation of survival. Figure 2-1 shows an overview of the treatment approaches used in patients with newly diagnosed MM.

Transplant-Eligible Patients

Depending on the transplant center, patients with MM up to age 65–75 without extensive comorbidities may be considered for ASCT. For these patients, initial treatment can be divided into four phases: induction, high-dose chemotherapy (HDT) with ASCT, consolidation, and maintenance. Allogeneic SCT is an option in patients with MM, but only through clinical trial circumstances because of the high risk of transplant-related mortality and morbidity related to graft-vs.-host disease. The risk of ASCT must be considered in light of the newer, especially safer chemotherapy treatment options.

Induction Therapy

The goal of induction treatment is to reduce the tumor burden to increase the ASCT complete remission rate and to

Table 2-2. MM Staging Systems

Stage	Durie-Salmon	Revised International Staging System (R-ISS)
I	Low cell mass: < 0.6 x 10^{12} cells/m^2 **plus all of the following:** • Hgb > 10 g/dL • Serum IgG < 5 g/dL • Serum IgA < 3 g/dL • Normal serum calcium (or ≤ 12 mg/dL) • Urine monoclonal protein excretion (Bence Jones) < 4 g/day • No generalized lytic bone lesions (solitary lesion OK)	B2M < 3.5 mg/L Albumin ≥ 3.5 g/dL AND Standard-risk chromosomal abnormalities by iFISH AND normal LDH
II	Neither stage I nor stage III	Neither stage I nor stage III
III	High cell mass: > 1.2 x 10^{12} cells/m^2 **plus one of more** of the following: • Hgb < 8.5 g/dL • Serum IgG > 7 g/dL • Serum IgA > 5 g/dL • Serum calcium > 12 mg/dL • Urine monoclonal protein excretion > 12 g/day • Advanced lytic bone lesions Staging is further classified as: A – SCr < 2 mg/dL B – SCr ≥ 2 mg/dL	B2M ≥ 5.5 mg/L AND Either high-risk chromosomal abnormalities by iFISH or high LDH
	Subclassification **A—Normal renal function (SCr < 2.0 mg/dL)** **B—Abnormal renal function (SCr ≥ 2.0 mg/dL)**	

B2M = β_2 microglobulin; iFISH = interphase fluorescence in situ hybridization; MM = multiple myeloma.

Information from: Durie BGM, Salmon SE. A clinical staging system for multiple myeloma. Cancer 1975;36:842-54; and National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Multiple Myeloma, version 3, 2016

decrease the plasma cell crowding of the BM to improve the quality of the graft. The ideal induction treatment will be well tolerated and will spare normal hematopoietic precursors so that the patient's stem cells can be mobilized successfully. Alkylating agents and other stem cell toxins are avoided because of their risk of hematopoietic toxicity. A decrease in $CD34^+$ cells may occur with lenalidomide treatment; therefore, after four cycles of treatment with lenalidomide-based regimens, stem cells must be collected for transplant-eligible patients.

Before the introduction of novel agents, standard induction regimens were either high-dose dexamethasone or a combination of dexamethasone with nonalkylating chemotherapy such as doxorubicin and vincristine (vincristine/doxorubicin/dexamethasone regimen). Table 2-5 lists the approved regimens used as induction for patients with MM and their mechanisms of action.

Bortezomib-Based Regimens

Bortezomib is a first-generation proteasome inhibitor (PI) that binds reversibly to the 20S domain of the proteasome. Several randomized trials have shown the superiority of induction regimens containing bortezomib compared with vincristine/doxorubicin/dexamethasone-based regimens. Therefore, vincristine/doxorubicin/dexamethasone is no longer the standard induction treatment (Harousseau 2010). Bortezomib in combination with dexamethasone showed improved event-free survival (EFS) and OS in patients with t(4;14) compared with vincristine/doxorubicin/dexamethasone or vincristine/doxorubicin/dexamethasone plus consolidation with dexamethasone/cyclophosphamide/etoposide/cisplatin. Patients with either t(4;14) or del(17p) (which is considered poor-risk cytogenetics) have a short EFS and OS. In a separate trial evaluating bortezomib and dexamethasone compared with vincristine/doxorubicin/dexamethasone, patients with del(17p) had no increased EFS or OS in the two arms (Table 2-6) (Avet-Loiseau 2010).

Several randomized trials have compared a two-drug regimen of thalidomide and dexamethasone or bortezomib and dexamethasone with the three-drug regimen of bortezomib, thalidomide, and dexamethasone. In the studies, bortezomib/thalidomide/dexamethasone was significantly superior to the two-drug regimen in achieving CR and VGPR rates, and

Table 2-3. Response Criteria in MM[a]

Response Criteria	IMWG
CR	Negative serum and urine immunofixation Disappearance of soft tissue plasmacytomas ≤ 5% plasma cells in BM Normal FLC ratio if disease only measurable that way
sCR	CR defined as above plus: Normal FLC ratio Absence of clonal cells in BM by immunohistochemistry or immunofluorescence
Immunophenotypic CR	sCR defined as above plus: Absence of phenotypically aberrant plasma cells in BM by multiparametric flow cytometry
Molecular CR	CR defined as above plus: Negative allele-specific oligonucleotide PCR
VGPR	Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein < 100 mg every 24 hr
PR	≥ 50% reduction in serum M-protein and ≥ 90% reduction in 24-hr urine M-protein or to 200 mg every 24 hr
MR	≥ 25% but ≤ 49% reduction in serum M-protein and reduction in 24-hr urine M-protein by 50%–89% If present at baseline, 25%–49% reduction in soft tissue plasmacytomas No increase in size or quantity of lytic bone lesions (development of compression fractures does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD	Increase of 25% from the lowest response in any of below: Serum M-protein, urine M-protein Development of new or definite increase in bone lesions Development of hypercalcemia not attributed to another disease

[a]sCR, CR, and PD criteria must be met on two separate assessments.

CR = complete response; MM = multiple myeloma; MR = minimal response; PD = progressive disease; PR = partial response; sCR = stringent complete response; SD = stable disease; VGPR = very good partial response.

Table 2-4. Relapse Criteria in MM

Relapse Category	IMWG
Clinical relapse	Requires at least one of the following: • Development of new bone lesions or soft tissue plasmacytoma • Increase in existing plasmacytomas or bone lesions (50% increase or ≥ 1 cm) Any of the following attributable to myeloma: a. Development of hypercalcemia (> 11.5 mg/dL) b. Development of anemia (drop in Hgb ≥ 2 g/dL) c. Rise in SCr (≥ 2 mg/dL)
Relapse from CR	Requires at least one of the following: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis • ≥ 5% plasma cells in the BM • Appearance of any other sign of progression (e.g., new plasmacytoma, new lytic bone lesion)

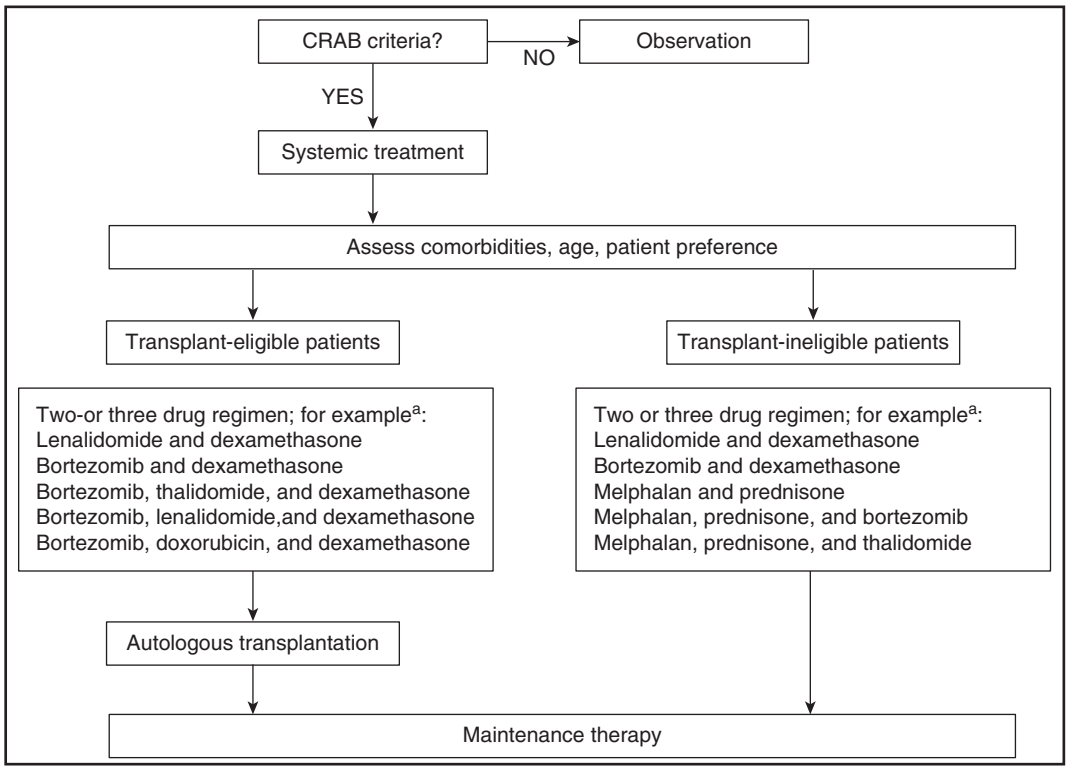

Figure 2-1. Clinical management of patients with newly diagnosed multiple myeloma.

[a]The listed therapy combinations are examples and are not inclusive of all regimens.

bortezomib/thalidomide/dexamethasone is considered a standard induction regimen. In the GIMEMA trial, patients received either thalidomide and dexamethasone or bortezomib, thalidomide, and dexamethasone as induction, followed by tandem ASCT with high-dose melphalan and then consolidation with the same primary regimen. Complete response or near-CR rates for the overall treatment protocol were achieved in 168 patients (71%, 95% CI 65·4–77·0) receiving bortezomib/thalidomide/dexamethasone and in 128 patients (54%, 95% CI 47·4–60·1) receiving a two-drug regimen of thalidomide and dexamethasone (p<0.0001) (Rosinol 2012; Cavo 2010).

Finally, several phase II trials have shown that cyclophosphamide/bortezomib/dexamethasone has high response rates in patients with newly diagnosed MM. In the German DSMM XIa study, cyclophosphamide/bortezomib/dexamethasone used as primary treatment had high response rates (overall response rate [ORR] 84% with 74% PR rate and 10% CR) (Tsukada 2015).

Bortezomib is dosed at 1.3 mg/m^2 intravenously or subcutaneously on days 1, 4, 8, and 11 of each 21-day cycle. Dose modifications exist for adverse events including neuropathy (see the Supportive Care section). Bortezomib in a once-weekly dose, perhaps associated with fewer toxicities, was studied in 2010. Patients treated with weekly bortezomib intravenously (part of a modified cyclophosphamide/bortezomib/dexamethasone regimen) achieved similar responses to the twice-weekly regimen (ORR 93% vs. 88%, VGPR 60% vs. 61%). Grade 3/4 adverse events were lower in the weekly regimen (37%/3% vs. 48%/12%), which translated into fewer dose reductions in the weekly regimen. Peripheral neuropathy (PN) was similar in both arms; however, the total dose per cycle was higher in the weekly than in the twice-weekly schedule (6 mg/m^2 vs. 5.2 mg/m^2). Therefore, once-weekly bortezomib is a viable option for patients with underlying neuropathy or based on physician and patient preferences (Reeder 2010).

Lenalidomide-Based Regimens

Lenalidomide is a second-generation immunomodulatory drug (IMiD) and a 50,000 times more potent analog of thalidomide. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer cells, production of increased numbers of natural killer T cells, and inhibition of proinflammatory cytokines (e.g., TNFα and IL-6) by monocytes. In MM cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis. Therefore, this regimen is recommended in

Table 2-5. Summary of MM Agents with Mechanism of Action and Approved Indication

Drug	MOA	AEs of Single Drug	Combination Regimens and Indication[a]
BOR IV or SC	PI; reversibly inhibits (β_1) caspase-like and (β_2) trypsin-like sites of 20S proteasome, but preferentially inhibits (β_5) chymotrypsin-like site	GI symptoms, thrombocytopenia, fatigue, and PN (less with SC than with IV dosing) Herpes zoster reactivation (antiviral prophylaxis recommended); dose adjustment needed for liver dysfunction	Single agent (maintenance) BOR/DEX (Induction all, R/R) BOR/DOX/DEX (Induction tx) VTD (Induction tx, R/R) CyBorD (Induction all, R/R) MPB (Induction non-tx) BOR/liposomal DOX (R/R)
LEN oral	Antiangiogenesis, immunomodulation, and inhibition of tumor necrosis factor-alpha Direct cytotoxicity by inducing free radical–mediated DNA damage Second-generation IMiD and more potent than thalidomide	Fatigue, rash, DVT (routine prophylaxis with aspirin or other anticoagulant in all patients) Diarrhea and leg cramps with long-term use Embryo-fetal toxicity Myelosuppression; dose adjustment needed for renal dysfunction and toxicities	Single agent (maintenance) LEN/DEX (Induction all, R/R) LEN/BOR/dEX (RVD) (Induction all, R/R) MPL (Induction non-tx)
CAR IV	Like BOR but an irreversible PI	GI symptoms, fatigue, thrombocytopenia, anemia, hypertension, dyspnea Serious cardiopulmonary toxicity in ~5%	CAR/LEN/DEX (Induction all, R/R) CAR/DEX (R/R)
POM oral	Like LEN, but more potent and third-generation IMiD	Fatigue, rash, myelosuppression DVT (routine prophylaxis with aspirin or other anticoagulant in all patients) Embryo-fetal toxicity; not studied in patients with SCr > 3 mg/dL	POM/DEX (R/R)
BEN	Alkylating agent	Neutropenia, thrombocytopenia, anemia, fatigue	Single agent (R/R) BEN/LEN/DEX (R/R)
Daratumumab IV	Monoclonal antibody targeting CD38	Infusion-related reactions, fatigue, anemia, nausea	Single agent (R/R)
ELO IV	Immunostimulatory monoclonal antibody targeting signaling lymphocytic activation molecule F7 (SLAMF7)	Infusion-related reactions, fatigue, infections	ELO/LEN/DEX (R/R)
PAN oral	PAN-deacetylase inhibitor; blocks aggresome pathway	Diarrhea, thrombocytopenia, fatigue	PAN/BOR/DEX (R/R)
IXA oral	Like BOR, first oral reversible PI	GI, fatigue, less neurotoxic than BOR	IXA/LEN/DEX (R/R)

[a]Includes FDA-approved and non–FDA-approved indications.

AE = adverse event; BEN = bendamustine; BOR = bortezomib; CyBorD = cyclophosphamide/bortezomib/dexamethasone; DEX = dexamethasone; DOX = doxorubicin; DVT = deep venous thrombosis; ELO = elotuzumab; IMiD = immunomodulatory drug; Induction tx = induction for transplant-eligible patients; Induction all = induction for patients eligible or ineligible for transplantation; Induction non-tx = induction for nontransplant-eligible patients; IV = intravenous(ly); IXA = ixazomib; LEN = lenalidomide; MM = multiple myeloma; MPB = melphalan/prednisone/bortezomib; PAN = panobinostat; POM = pomalidomide; PI = proteasome inhibitor; PN = peripheral neuropathy; R/R = relapsed/refractory; RVD = lenalidomide/bortezomib/dexamethasone; SC = subcutaneous(ly).

Table 2-6. BOR- and CAR-Based Regimens for Induction in Transplant-Eligible Patients

Regimen	n	Results	AEs
VAD vs. BOR/DEX 2005-01 trial (Harousseau 2010)	121 vs. 121 Phase III	ORR 62.8% vs. 78.5%[a] CR/near-CR 6.4% vs. 14.8%[a] VGPR 15.1% vs. 37.7%[a]	Hematologic toxicity and deaths more often in VAD group; PN grades 3/4; 2.5% vs. 9.2%
VAD vs. BOR/DEX (Avet-Loiseau 2010)	98 vs. 106 patients with t(4;14) Retrospective	EFS 16 mo vs. 28 mo[a] 4-yr OS 32% vs. 63%[a]	Not reported
TD vs. VTD GIMEMA Italian group (Cavo 2010)	239 vs. 241 Phase III	CR/near-CR 11% vs. 31%[a] 3-yr OS 84% vs. 86%	PN 2% vs. 10%[a] (IV BOR used); grade 3/4 toxicities were higher in VTD group (56% vs. 33%)
TD vs. VTD PETHEMA/GEM Spanish group (Rosinol 2012)	127 vs. 130 Phase III	CR 14% vs. 35%[a] CR 0% vs. 35%[a] (in high-risk cytogenetic patients)	PN grades 3/4; 5% vs. 14%[a]
CyBorD (Reeder 2010)	33 Phase II	ORR 88% VGPR 61% CR/near-CR 39% 5-yr PFS 42%; 5-yr OS 70%	Grade 3 AEs 48% Grade 4 AEs 12%
CAR/LEN/DEX (Jakubowiak 2012)	53 Phase I/II	Near-CR 62% sCR 42% 24 month PFS 92%	Grade 3/4 hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), neutropenia (17%)
CAR/LEN/DEX (Korde 2015)	45 Phase II	PFS 83.3% (median follow-up 10 mo)	Grade 3/4 electrolyte disturbances (18%), liver function test elevation (13%), rash (11%), fatigue (11%), anemia (16%), leukopenia (13%), thrombocytopenia (11%)

[a]Statistically significant; ORR.

EFS = event-free survival; ORR = overall response rate; PFS = progression-free survival; R/R = relapsed/refractory; TD = compared a two-drug regimen of thalidomide and dexamethasone; VAD = vincristine/doxorubicin/dexamethasone.

Information from: Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621-9; Avet-Loiseau H, Leleu X, Roussel M, et al. Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p). J Clin Oncol 2010;28:4630-4; Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075-85; Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120:1589-96; Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood 2010;115:3416-7; Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012;120:1801-9; and Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol 2015;1:746-54.

the treatment of patients with newly diagnosed MM as part of induction therapy.

An open-label trial of 445 patients with MM randomized patients to receive either lenalidomide plus high-dose dexamethasone (40 mg days 1–4, 9–12, and 17–20 of a 28-day cycle) or lenalidomide plus low-dose dexamethasone (40 mg on days 1, 8, 15, and 22 of a 28-day cycle) for four cycles and then either undergo ASCT or continue treatment until progression. At the 1-year interim analysis, OS was 96% in the low-dose dexamethasone group versus 87% in the high-dose group (p=0.0002). The 2-year OS was 87% versus 75%, respectively. The cause of the inferior OS with high-dose dexamethasone was related to the increased number of deaths as the result of higher toxicity rates. Grade 3/4 toxicity within the first 4 months occurred in 52% of patients in the high-dose arm versus 35% in the low-dose arm. Toxicities observed included

higher rates of deep venous thrombosis (DVT), infections including pneumonia, and fatigue (26 vs. 12%, 16 vs. 9%, and 15 vs. 9%, respectively). Because of higher toxicity rates, high-dose dexamethasone is not recommended as part of an induction regimen for patients with newly diagnosed MM (Rajkumar 2010). See the Supportive Care section for more information on the prevention of lenalidomide-related DVT.

Another regimen recommended by the NCCN guidelines for the treatment of patients with newly diagnosed MM is lenalidomide/bortezomib/dexamethasone. In a phase I/II study, response rates were 100% with 74% VGPR or better and 52% CR/near-CR in patients with newly diagnosed MM (Richardson 2010). In the Intergroupe Francophone du Myélome (IFM) 2008 phase II study, patients received lenalidomide/bortezomib/dexamethasone as induction, followed by ASCT, and two more cycles of consolidation with lenalidomide/bortezomib/dexamethasone, followed by 1 year of lenalidomide maintenance. A VGPR rate or better was 58% at completion of induction. Post-transplantation, the VGPR rate was 70% or better, and the post-consolidation VGPR rate was 87% (Roussel 2014). Lenalidomide is a 25-mg oral daily dose taken on days 1–21 of a 28-day cycle. Dose modifications are based on toxicities, and lenalidomide requires a Risk Evaluation and Mitigation Strategies program in which the providers must register in order to prescribe the drug. Because of the risk of embryo-fetal toxicity, women of childbearing potential must adhere to frequent, extensive pregnancy testing.

Carfilzomib-Based Regimens

Carfilzomib is a second-generation PI that binds with high selectivity and irreversibility to the chymotrypsin-like activity of the 20S proteasome, leading to cell cycle arrest and apoptosis. Carfilzomib lacks neurodegeneration in vitro and is less neurotoxic than bortezomib.

The safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone for primary treatment of MM was studied in two single-arm studies. A phase I/II study evaluated 53 transplant-eligible patients who received carfilzomib (20, 27, or 36 mg/m^2 on days 1, 2, 8, 9, 15, and 16 and days 1, 2, 15, and 16 after cycle 8 for another eight cycles) with lenalidomide 25 mg/day on days 1–21 and dexamethasone 40 mg weekly for cycles 1–4, followed by 20 mg weekly for cycles 5–8 in 28-day cycles. After cycle 24, maintenance with single-agent lenalidomide was recommended off study (Jakubowiak 2012). In another study, 45 transplant/nontransplant-eligible patients received carfilzomib 20 or 36 mg/m^2 (20 mg/m^2 on days 1 and 2 of cycle 1 only) on days 1, 2, 8, 9, 15, and 16 with lenalidomide 25 mg/day on days 1–21 and dexamethasone 20 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 for cycles 1–4, then decreased to 10 mg for cycles 5–8. After eight cycles, patients with stable disease received up to 24 cycles of extended lenalidomide 10 mg/day on days 1–21 (Korde 2015).

Given the study outcomes from these two trials, the NCCN guidelines recommend the carfilzomib/lenalidomide/dexamethasone regimen as an option for transplant-eligible patients with newly diagnosed MM (NCCN category 2A).

Autologous Transplantation

After patients receive four to six cycles of induction therapy, response is assessed. Stem cells are collected through a procedure called apheresis. Patients receive single-agent filgrastim, filgrastim and plerixafor, or cyclophosphamide followed by filgrastim before apheresis. Stem cells are collected over several days until the amount of stem cells (about 5 x 10^6 CD34$^+$ cells/kg) collected is sufficient to support two ASCTs. The objective of ASCT is to support the HDT required to reduce the duration and toxicity of severe myelosuppression. Use of ASCT improves CR rates and prolongs median OS in MM by about 12 months; its treatment-related mortality is 1%–2%. Eligibility is based on age, performance status, and comorbidities.

The preferred conditioning regimen (HDT) is melphalan at a dose of 200 mg/m^2. The ASCT after the melphalan-conditioning regimen prevents severe neutropenia and toxicity, which can cause very high mortality rates. The IFM group was the first to conduct a randomized trial showing the superiority of HDT/ASCT to conventional chemotherapy in patients younger than 65. These findings were confirmed 7 years later in a larger study conducted by the UK Medical Research Council. Given the results from the IFM group and the UK Medical Research Council, HDT/ASCT is the new standard of care in patients younger than 65 without severe comorbidities. Overall, seven randomized trials have compared HDT/ASCT with conventional chemotherapy. Although EFS was superior with HDT/ASCT in five of the seven trials, OS was prolonged significantly in only three trials. These trials were conducted before the introduction of novel agents; therefore, the role of transplantation may evolve in the future with the introduction of the newer agents. Currently, NCCN recommends ASCT for the treatment of primary progressive or refractory disease post-primary therapy. Four randomized trials found that survival is similar whether ASCT is done early (after four cycles of induction) or delayed (at the time of relapse). A recent trial by IFM and the Dana-Farber Cancer Institute compared early versus delayed ASCT in patients treated with lenalidomide/bortezomib/dexamethasone as induction. Patients were randomized to receive either lenalidomide/bortezomib/dexamethasone or lenalidomide/bortezomib/dexamethasone (three cycles), followed by ASCT, and then lenalidomide/bortezomib/dexamethasone consolidation (two cycles) or lenalidomide/bortezomib/dexamethasone for eight cycles with ASCT reserved at relapse. Both arms received lenalidomide maintenance for 1 year. Progression-free survival (PFS) was significantly improved in the early ASCT arm, but this did not translate into OS benefit. The trial also found that the 3-year OS in both arms was very high, which reflects the remarkable improvement in

therapy with the incorporation of these novel therapies (Attal 2015). Patients with intermediate- or high-risk MM may benefit from early transplantation, according to studies that found that patients with t(4;14) and del(17p) receiving early ASCT achieved outcomes closer to those of standard-risk patients in trials (NCCN 2016; Sonneveld 2012).

Transplant-Ineligible Patients

Many treatment options are available for patients with newly diagnosed MM who are not eligible for transplantation. The primary goals in these patients are to reduce the tumor burden and prolong survival. Many of the regimens used for induction therapy for transplant-eligible patients can also be used in nontransplant-eligible patients. In addition, melphalan-based therapy is of benefit and is well tolerated.

Two phase III studies (IFM 01-01 and HOVON group) compared melphalan plus prednisone with melphalan/prednisone plus thalidomide. In the IFM 01-01 study, 232 patients with newly diagnosed disease older than 75 received melphalan 0.2 mg/kg/day plus prednisone 2 mg/kg/day on days 1–4 every 6 weeks (total of 12 cycles of therapy). During the study, 113 patients were randomized to receive 100 mg/day of oral thalidomide, and 116 patients received placebo for 72 weeks. The median OS at the follow-up of 47.5 months was significantly improved in the melphalan/prednisone plus thalidomide arm (44 months) compared with the melphalan/prednisone arm (29.1 months; p=0.028). Median PFS was significantly longer in the melphalan/prednisone plus thalidomide group than in the melphalan/prednisone group (24.1 months vs. 18.5 months; p=0.001). Adverse events were significantly increased in the melphalan/prednisone plus thalidomide arm, in which grade 3/4 neutropenia was 23% in the melphalan/prednisone plus thalidomide arm and 9% in the melphalan/prednisone arm (p=0.003), and grade 2–4 PN was 20% in the melphalan/prednisone plus thalidomide arm and 5% in the melphalan/prednisone arm (p<0.001) (Hulin 2009).

The HOVON-49 is a randomized phase III trial comparing standard melphalan/prednisone (n=168) with melphalan/prednisone plus thalidomide (n=165) (thalidomide 200 mg/day as induction) in 333 patients with newly diagnosed MM older than 65. Results showed significantly higher response rates in melphalan/prednisone plus thalidomide-treated patients than in melphalan/prednisone-treated patients, and the ORR (> or = PR) was 66% versus 45%, respectively (p<0.001). The EFS was 13 months with melphalan/prednisone plus thalidomide versus 9 months with melphalan/prednisone (p<0.001). The OS was 40 months with melphalan/prednisone plus thalidomide versus 31 months with melphalan/prednisone (p=0.05). Adverse events of grade 2 or higher occurred in 60% of patients receiving melphalan/prednisone compared with 87% of patients receiving melphalan/prednisone plus thalidomide. Peripheral neuropathy, a known adverse effect of thalidomide, occurred in 23% of patients in the melphalan/prednisone plus thalidomide arm at grades 3/4. Venous thrombotic events, another well-known adverse effect of thalidomide, occurred in 10% of patients receiving melphalan/prednisone plus thalidomide versus 1% of patients receiving melphalan/prednisone (Wijermans 2010).

The VISTA trial was a large randomized international phase III study that evaluated 682 patients receiving melphalan/prednisone versus melphalan/prednisone/bortezomib. The trial evaluated previously untreated patients with MM who were 65 and older or patients younger than 65 and not eligible for transplantation. Patients were randomized to melphalan/prednisone or melphalan/prednisone/bortezomib-338 and melphalan/prednisone/bortezomib-344, respectively. Melphalan (9 mg/m^2) and prednisone (60 mg/m^2) were given orally on days 1–4, either alone or with bortezomib (1.3 mg/m^2) on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1–4 and on days 1, 8, 22, and 29 during cycles 5–9 every 6 weeks for a total of nine cycles. Results showed a 31% reduced risk of death with melphalan/prednisone/bortezomib versus melphalan/prednisone with a median follow-up of 60.1 months (p<0.001). Median OS was 56.4 months with melphalan/prednisone/bortezomib versus 43.1 months with melphalan/prednisone, with 5-year OS rates of 46% with melphalan/prednisone/bortezomib versus 34.4% with melphalan/prednisone. Patients relapsing after bortezomib therapy were not resistant to subsequent therapies and could successfully be treated with immunomodulator-based therapy supporting bortezomib as a frontline treatment (San Miguel 2013b).

No head-to-head trials compare melphalan/prednisone plus thalidomide with melphalan/prednisone/bortezomib. A meta-analysis of the phase III trials shows that better response rates can be expected with melphalan/prednisone/bortezomib than with melphalan/prednisone plus thalidomide, making melphalan/prednisone/bortezomib the preferred regimen in this patient population (Yeh 2008).

Maintenance Regimens

In an effort to delay disease progression and prolong survival, researchers have been exploring the use of agents such as thalidomide, lenalidomide, and bortezomib, as maintenance. Ideally, maintenance therapy should sustain treatment responses, have good safety and tolerability profiles in long-term use, and be convenient for patients.

Thalidomide

Many phase III trials have evaluated thalidomide use as maintenance therapy in MM (Table 2-7). In most of these studies, the drug was continued until disease progression or relapse. Regardless of the duration, thalidomide-based therapy in all of these trials led to improvements in EFS and/or PFS. However, only two studies reported an OS benefit.

In the IFM 99-02 study, patients without progressive disease after a double ASCT were randomized to one of three treatment arms: (1) no maintenance, (2) pamidronate 90 mg at 4-week intervals, or (3) thalidomide 400 mg daily (with a

Patient Care Scenario

L.M. is a 60-year-old woman who presents for a routine physical examination. She has no complaints except for mild pain in her left leg. Physical examination reveals that she is mildly anemic (Hgb 10.4 g/dL, decreased from 13.8 g/dL the previous year). She had a normal colonoscopy 1 year ago, and additional laboratory testing confirms that she is not iron-deficient. Serum protein electrophoresis and immunofixation reveal an IgG1κ monoclonal protein of 2.87 g/dL with reduced concentrations of IgA and IgM. A skeletal survey reveals several lytic bone lesions (with the largest lesion in the left femur) but no fracture. What are the next steps in treating this patient, in whom MM is suspected?

ANSWER

Although this patient with an elevated serum monoclonal protein concentration and immunoparesis (decreased concentrations of IgA and IgM), anemia, and lytic bone lesions likely has MM, confirmation is needed by a BM biopsy. Bone marrow biopsies have 10% or greater plasma cells in patients with MM, together with one or more physical symptoms. She does not meet the criteria for SMM because she has several lytic bone lesions and mild anemia, according to the CRAB criteria. Cytogenetic analysis should be done, including FISH for common abnormalities such as deletion of chromosome 13; this test provides important prognostic information. The patient meets the criteria for systemic anti-myeloma therapy, but this should not be initiated until the diagnostic workup is completed. Once the diagnostic workup and staging are complete, L.M.'s treatment plan will be based on transplant eligibility. Because she is young with a good performance status (PS 0 or 1), autologous transplantation is an option.

L.M. will be treated with four to six cycles of an induction therapy (see Table 2-5). After four cycles of treatment, the patient's stem cells will be mobilized. After six cycles, she will be ready to undergo an ASCT. It is important to consider supportive care adjuncts while treating this patient. A bisphosphonate should be incorporated into the anti-myeloma treatment plan. If the patient will start bortezomib therapy, acyclovir prophylaxis should be initiated, and anticoagulation should be initiated with IMiD therapy.

1. National Comprehensive Cancer Network (NCCN). National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Multiple Myeloma, version 3, 2016.
2. Hameed A, Brady JJ, Dowling P, et al. Bone disease in multiple myeloma: pathophysiology and management. Cancer Growth Metastasis 2014;7:33-42.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.

Table 2-7. Phase III Trials of Thalidomide as Maintenance

Study	ASCT	Study Arms	Maintenance Duration	Effect of Thalidomide
Attal (n=597)	Y	No maintenance vs. pamidronate vs. thalidomide + pamidronate	Until progression	Improved OS and EFS (p < 0.04; p<0.009)
Barlogies (n=668)	Y	Interferon + DEX vs. thalidomide	Until relapse or toxicity	Improved EFS (p=0.01); no difference in OS
Lockhorst (n=556)	Y	Interferon vs. thalidomide	Until progression or relapse	Improved EFS and PFS (p=0.001); no difference in OS
Morgan (n=820)	Y	No maintenance vs. thalidomide	Until relapse	Improved PFS in patients achieving < VGPR (p=0.007); no difference in OS
Stewart (n=332)	Y	Thalidomide + prednisone vs. observation	Until progression	Improved median PFS (p<0.0001); no difference in OS
Ludwig (n=128)	N	Thalidomide + interferon vs. interferon	Until progression or intolerance	Improved PFS (p=0.0068); no difference in OS
Spencer (n=269)	Y	Prednisone vs. thalidomide + prednisone	12 mo	Improved 3-yr PFS and OS (p<0.001; p=0.004)

ASCT = autologous stem cell transplantation.

dose reduction for toxicity allowed to a minimum dose of 50 mg/day) plus pamidronate. The median duration of maintenance therapy was 15 months (range 0.1–50 months). Results showed prolonged survival in patients receiving thalidomide plus pamidronate. In a study by Spencer and colleagues, patients with stable disease or better (PR or VGPR or CR) after a single ASCT were randomized to one of two maintenance regimens: (1) prednisone 50 mg every other day indefinitely or until progression or (2) prednisone plus thalidomide 100 mg daily (with dose escalation to 200 mg if tolerated, for up to 12 months). The investigators reported superior PFS and OS for the patient group receiving thalidomide-based maintenance. Therapy duration was not the same in these two studies, yet both reported an OS benefit. Therefore, the optimal duration of thalidomide maintenance is still unclear. Of interest, in three studies of thalidomide-based maintenance, only patients who achieved less than a VGPR benefited from this therapy. In one of these studies, the investigators explained their observation by suggesting that thalidomide further reduces tumor mass after the high-dose therapy given to patients undergoing ASCT. Therefore, patients with a greater tumor mass after transplantation (i.e., those achieving less than VGPR) have a greater benefit from thalidomide maintenance. It may be helpful to factor in these findings when determining the maintenance duration with thalidomide to protect against treatment resistance and minimize adverse effects such as PN, which is commonly associated with long-term use of this agent (NCCN 2016; Spencer 2009; Attal 2006).

Lenalidomide

Lenalidomide, which has a better tolerability profile than thalidomide, continues to be evaluated as maintenance in several clinical trials (Table 2-8). In the phase III IFM 2005-02 and CALGB 100104 trials, transplant-eligible patients with stable disease were randomized to lenalidomide maintenance versus placebo after ASCT until disease relapse or progression. Treatment with lenalidomide significantly prolonged PFS and time to progression, though no difference in OS was reported. In the IFM 2005-02 trial, investigators reported that the benefit of lenalidomide maintenance was observed across subgroups stratified by response after transplantation in patients achieving VGPR or greater, as well as in those with a poorer posttransplant response.

Similar findings occurred in two phase III studies, in which older adult patients who had not undergone transplantation received lenalidomide maintenance after initial treatment with a lenalidomide-based regimen. These data suggest that continuous use of lenalidomide extends PFS compared with placebo. However, this benefit is accompanied by a high incidence of grade 3/4 hematologic adverse events, as reported in two of the three cited studies (grade 3/4 hematologic toxicity statistically significant $p<0.001$), as well as an increased incidence of secondary malignancies. In the IFM 2005-02 trial, 32 of 307 patients receiving lenalidomide developed second primary malignancies, including 6 who developed B-cell malignancies (i.e., acute lymphocytic leukemia and Hodgkin disease), compared with 12 of 307 in the placebo group ($p=0.002$). The cumulative incidence of secondary malignancies began to develop after 24 months of treatment. Several factors are correlated with an increased probability of developing a second cancer, including treatment with the combination regimen of dexamethasone, cyclophosphamide, etoposide, and cisplatin, as well as patient age and sex. In the CALGB 100104 study evaluating lenalidomide maintenance, 24 new cancers were reported. In the lenalidomide arm (n=231),

Table 2-8. Phase III Trials of LEN as Maintenance

Study	ASCT	Study Arms	Maintenance Duration	Effect of LEN
Attal (n=614)	Y	LEN vs. placebo	Until relapse	Improved PFS ($p<0.001$); no difference in OS
McCarthy (n=460)	Y	LEN vs. placebo	Until progression	Significantly improved TTP and a reduction in risk of progression ($p<0.0001$); no significant difference in number of deaths
Palumbo (n=459)	N	LEN vs. placebo	Until progression	Improved PFS and OS with MPR-R vs. MPR vs. MP ($p<0.001$) 3-yr OS 70%, 62%, 66% for MPR-R vs. MPR vs. MP
Benboubker (n=1623)	N	LEN/DEX (Rd cont.) vs. LEN/DEX (Rd) vs. MPT	Until progression 72 wk 72 wk	Improved median PFS for Rd cont. ($p<0.001$) 4-yr OS 59%, 56%, 51% for Rd cont. vs. Rd 72 wk, vs. MPT

MP = melphalan, prednisone; MPR = melphalan/prednisone/lenalidomide; MPR-R = MPR with continued lenalidomide; MPT = melphalan/prednisone plus thalidomide; TTP = time to progression.

Table 2-9. Phase III Trials of BOR as Maintenance

Study (n)	ASCT	Study Arms	Maintenance Duration	Effect of LEN
Sonneveld (626)	Y	BOR vs. thalidomide	2 yr	Improved PFS and OS (p=0.047; p=0.048)
Palumbo (511)	Y	BOR + thalidomide vs. no maintenance	2 yr or until progression or relapse	Significantly improved 3-yr PFS in maintenance arm (p=0.008); no difference in OS

BOR = bortezomib.

Information from Sonneveld P, Schmidt-Wolf IG, Van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 2012,30:2946-55; and Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. J Clin Oncol 2010;28:5101-9.

8 patients developed hematologic cancers and 10 developed solid cancers; in the placebo arm (n=229), six patients developed cancer. The rates of secondary cancers reported with melphalan/prednisone, melphalan/prednisone/lenalidomide, and melphalan/prednisone/lenalidomide-lenalidomide maintenance in the MM-015 trial of nontransplant patients were 2.6%, 5.9%, and 8%, respectively (Attal 2012; McCarthy 2012; Palumbo 2012).

Bortezomib

Results of two large phase III trials have also had encouraging results with bortezomib maintenance therapy (Table 2-9). In both trials, the maintenance duration was 2 years. In the HOVON-65/GMMG-HD4 study, transplant-eligible patients were randomized to vincristine/doxorubicin/dexamethasone or bortezomib, doxorubicin, and dexamethasone. After transplantation, patients in the vincristine/doxorubicin/dexamethasone arm received thalidomide maintenance dosed at 50 mg/day, and those in the bortezomib/doxorubicin/dexamethasone arm received bortezomib maintenance dosed at 1.3 mg/m^2 every 2 weeks. At 24 months, more patients remained on maintenance therapy in the bortezomib/doxorubicin/dexamethasone-bortezomib arm (49%) than in the vincristine/doxorubicin/dexamethasone-thalidomide arm (29%). In addition, only 9% of patients who received bortezomib/doxorubicin/dexamethasone-bortezomib had grade 3/4 PN, compared with 15% of those who received vincristine/doxorubicin/dexamethasone-thalidomide. The median PFS was 36 months in the bortezomib/doxorubicin/dexamethasone-bortezomib arm versus 27 months in the vincristine/doxorubicin/dexamethasone-thalidomide arm (HR 0.75; p=0.005), which also translated to a significant improvement in OS (HR 0.73; p=0.02). In a 2010 study, nontransplant patients were randomized to receive nine cycles of induction with a four-drug regimen of bortezomib intravenously, melphalan, prednisone, and thalidomide (VMPT), followed by maintenance with bortezomib intravenously and thalidomide (VT) or a three-drug induction regimen of VMP without maintenance. The doses of VMP in both induction arms were identical, and the VT maintenance therapy consisted of bortezomib 1.3 mg/m^2 every 2 weeks plus thalidomide 50 mg/day. Early in this trial, the bortezomib dosage was lowered in both the VMP and VMPT regimens from twice weekly to once weekly to minimize PN. In patients treated with VMPT-VT compared with VMP alone, grade 3/4 neutropenia occurred in 38% versus 28% (p=0.02), cardiac events occurred in 10% versus 5% (p=0.04), and thromboembolic events occurred in 5% versus 2% (p=0.08 not significant). More patients in the VMPT-VT group (21%) than in the VMP group (16%) discontinued treatment because of adverse events. However, the change to the weekly intravenous injection of bortezomib significantly decreased the rates of PN (14% twice weekly vs. 2% once weekly) and discontinuation because of this toxicity (16% twice weekly vs. 4% once weekly), with no significant change in efficacy (Sonneveld 2012; Palumbo 2010).

Salvage Therapy for Patients with Relapsed/Refractory MM

There are many choices of therapy for patients with MM in the relapsed/refractory (R/R) setting (see Table 2-5). In this chapter, R/R is used interchangeably because these patients are treated in the same way.

Treatment of patients with R/R MM is heterogeneous because the therapeutic choices at this stage are affected by patient status, disease characteristics, exposure to previous drugs, therapeutic effect, and toxicities. With each relapse, MM becomes more difficult to treat because of the emergence of resistant clones, until the disease becomes completely refractory to any available treatment. With each treatment course, patients tend to become more vulnerable to toxicities and therefore may not tolerate additional therapy.

Although relapsed disease is progression based according to the criteria in Table 2-3, refractory MM is defined as disease that progresses on salvage therapy or progresses within 60 days of the last treatment in patients who previously achieved at least a minimal response to treatment.

Progressive disease could be present as biochemical or clinical relapse (Table 2-4 and Table 2-5). Once progression is confirmed through a diagnostic workup, the decision to use a previously used or new regimen will be made. This decision is guided by the response duration and the tolerability of the previous regimen. With early relapse (6–12 months) after treatment discontinuation, the patient will receive new therapy. With longer response duration, retreating with a previously used regimen can be considered. If a patient relapses while treated with an IMiD as maintenance therapy, a new agent can be added to the existing regimen as part of the treatment. In addition, patients who did not undergo ASCT after first response can be considered for an ASCT at first relapse, if eligible.

Although therapy duration is well defined in patients with newly diagnosed MM, optimal treatment duration is not well studied in the R/R setting. Patients with aggressive disease characteristics at relapse will likely progress and require continuous treatment. In general, these patients without comorbidities are treated with three- or four-drug combinations to achieve maximal response. They can be considered for ASCT, if eligible. Allogeneic SCT is an option for young patients with a matched donor, chemotherapy-sensitive disease, and excellent performance status (patient is fully active and able to do all pre-disease performance activities without restriction). Patients with indolent disease could be considered for ASCT, treated with maintenance, or carefully observed for a period without therapy. However, careful observation is sometimes risky because the disease can rapidly progress to become an aggressive phenotype (NCCN 2016).

Immunomodulatory Drugs

Thalidomide was the first IMiD used in refractory MM in the 1990s, and several subsequent studies confirmed its activity in patients with MM. However, prolonged use of thalidomide is associated with many adverse effects, including irreversible PN. Years later, lenalidomide was approved for relapsed MM as a second-generation IMiD, according to two randomized trials (MM-009 and MM-010) that evaluated lenalidomide 25 mg/day for 21 of 28-day cycles plus high-dose dexamethasone, compared with dexamethasone alone. Lenalidomide/dexamethasone significantly improved response rates, time to progression, and OS. Patients received either high-dose dexamethasone (20 mg days 1–4, 9–12, and 17–20) or low-dose dexamethasone 20 mg given weekly. The lenalidomide/high-dose dexamethasone had more adverse effects than did the lenalidomide/low-dose dexamethasone group, with the same efficacy. As a result, high-dose dexamethasone is no longer used in treatment regimens. In addition, dexamethasone single-agent treatment, which was used for patients with MM in the past, is no longer used with the availability of newer agents (Dimopoulos 2007; Weber 2007).

Pomalidomide is a third-generation IMiD. Like thalidomide and lenalidomide, pomalidomide has synergistic effects when combined with dexamethasone. In the multicenter phase III trial MM-003, patients with end-stage MM whose treatment with both lenalidomide and bortezomib failed were randomized to receive pomalidomide/dexamethasone or high-dose dexamethasone alone. In this highly pretreated patient group, ORR was 31% with pomalidomide/dexamethasone versus 10% in the patients taking dexamethasone. Compared with high-dose dexamethasone, PFS and OS were significantly prolonged in the pomalidomide/dexamethasone arm, with the median duration of response of 7 months in responding patients. Because of these results, pomalidomide/dexamethasone was approved in the relapse setting (San Miguel 2013a).

Proteasome Inhibitors

Bortezomib was FDA approved for patients with MM in the relapsed setting, according to two phase II studies (SUMMIT and CREST). The phase III APEX trial confirmed the efficacy of single-agent bortezomib for patients with relapsed MM. This study included 669 patients randomized to either bortezomib intravenously or high-dose dexamethasone. Overall response rate, median time to progression, and 1-year OS were significantly improved with bortezomib. Bortezomib showed activity in patients with chromosomal abnormalities such as del(13) and t(4;14), which are high-risk features, and patients with these chromosomal abnormalities have a worse prognosis. Similar to the IMiDs, adding dexamethasone to bortezomib is synergistic and can be used if patients can tolerate it (Jagannath 2007; Richardson 2007).

Because of the concerns for PN, a phase III study compared the safety and efficacy of subcutaneous versus intravenous bortezomib in patients with R/R MM. Bortezomib subcutaneously was noninferior in efficacy to intravenous administration with an improved safety profile. This study followed 222 patients with R/R MM who received bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 every 21 days up to eight cycles given intravenously or subcutaneously. At a median follow-up time of about 17 months, time to progression and OS were comparable for patients in both arms. Peripheral neuropathy was significantly reduced in the subcutaneous arm (all grade 38% vs. 53% (p=0.044); grade 3 or worse 6% vs. 16% (p=0.026). Because of these results, bortezomib is now also FDA approved for subcutaneous administration as frontline therapy for patients with newly diagnosed MM (Moreau 2011).

The success of bortezomib has stimulated the development of several novel PIs, including carfilzomib. Carfilzomib is approved in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with R/R MM who have received one to three lines of therapy and as a single agent. In a phase II trial, 266 patients were premedicated

with low-dose dexamethasone and received single-agent carfilzomib 20 mg/m^2 intravenously twice weekly for 3 of the 4 weeks in cycle 1, followed by 27 mg/m^2 for up to 12 cycles. The ORR was 23.7% with a median duration of response of 7.8 months. Median OS was 15.6 months. On average, patients had received a median of five prior regimens, and 80% were refractory to or intolerant of both bortezomib and lenalidomide. The most common adverse reactions with an incidence of 30% or greater were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia (Siegel 2012).

The ENDEAVOR study showed a 2-fold improvement in median PFS for patients with R/R MM who received carfilzomib/dexamethasone compared with patients who received bortezomib/dexamethasone (18.7 months vs. 9.4 months; p<0.0001). The carfilzomib arm received carfilzomib on days 1, 2, 8, 9, 15, and 16 of a 28-day cycle (20 mg/m^2 on days 1 and 2 [cycle 1]; 56 mg/m^2 thereafter) and dexamethasone (20 mg) on days 1, 2, 8, 9, 15, 16, 22, and 23. The bortezomib arm received bortezomib (1.3 mg/m^2; intravenously or subcutaneously on days 1, 4, 8, and 11 of a 21-day cycle) and dexamethasone (20 mg) on days 1, 2, 4, 5, 8, 9, 11, and 12. Grade 3 or higher adverse events in the carfilzomib/dexamethasone arm compared with the bortezomib/dexamethasone arm included hypertension (8.9% vs. 2.6), dyspnea (5.6% vs. 2.2%), cardiac failure (4.8% vs. 1.8%), and acute renal failure (4.1% vs. 2.6%). Given the results of this trial, carfilzomib/dexamethasone is now approved for patients with R/R MM (Dimopoulos 2016a).

Combination carfilzomib, lenalidomide, and low-dose dexamethasone is therapy approved for use in R/R MM. In the ASPIRE phase III trial, 792 patients were randomly assigned to carfilzomib/lenalidomide/dexamethasone (carfilzomib group) or lenalidomide/dexamethasone (control group). Carfilzomib was given on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m^2 on days 1 and 2 of cycle 1; 27 mg/m^2 thereafter) during cycles 1–12 and on days 1, 2, 15, and 16 during cycles 13–18, after which carfilzomib was discontinued. Lenalidomide (25 mg) was given on days 1–21. Dexamethasone (40 mg) was given on days 1, 8, 15, and 22. The PFS was significantly improved with carfilzomib (median 26.3 vs. 17.6 months; p=0.0001). The median OS was not reached in either group at the interim analysis. The ORR was 87.1% and 66.7% in the carfilzomib and control groups, respectively (p<0.001). Adverse events of grade 3 or higher were reported in 83.7% and 80.7% of patients in the carfilzomib and control groups. Rates of hypertension and venous thrombosis were higher in the carfilzomib group (Stewart 2015).

Other Regimens

Bendamustine is used as a single agent or in combination with lenalidomide and dexamethasone in R/R MM. In a dose-escalation study of bendamustine in 31 patients up to age 70 (bendamustine dose 60–100 mg/m^2), the ORR was 55% with a PFS of 26 weeks for all patients and 36 weeks for patients who received the higher dose (90–100 mg/m^2). Toxicity was mild and largely hematologic. In a phase I/II study involving 29 patients with R/R MM, lenalidomide plus bendamustine and dexamethasone had a PR of 52% and a VGPR of 24%. The median PFS was 6.1 months, with a 1-year PFS of 20%. Common toxicities included neutropenia, thrombocytopenia, anemia, and fatigue (Knop 2005).

Dexamethasone and thalidomide plus cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE) is a salvage therapy that combines high-dose dexamethasone (40 mg orally daily for 4 days) with thalidomide at 100 mg/day continuously and a 4-day continuous infusion of cisplatin (10 mg/m^2/day), doxorubicin (10 mg/m^2/day), cyclophosphamide (400 mg/m^2/day), and etoposide (40 mg/m^2/day). Cycles are usually administered every 4–6 weeks, and two to four cycles are planned. This extremely myelosuppressive regimen is commonly used as a last salvage treatment because some drugs have not been adequately studied in R/R MM.

Bortezomib intravenously (1.0 mg/m^2 on days 1, 4, 8, and 11) could be used with DT-PACE. This regimen has been evaluated in 16 patients with R/R MM in whom DT-PACE was administered (VDT-PACE). The ORR was 63%, and median PFS was 7 months. Hematologic toxicity was common, including grade 3/4 neutropenia (56%) and febrile neutropenia (56%) (NCCN 2016).

NEW THERAPIES FOR R/R MM

The FDA approved four new agents for the treatment of R/R MM in 2015. In February, the FDA approved panobinostat (Farydak), the first histone deacetylase inhibitor to receive FDA approval. In November, the FDA accelerated the approval of daratumumab (Darzalex), the first-ever monoclonal antibody and immunotherapy for MM. In December, the second monoclonal antibody and immunotherapy option, elotuzumab (Empliciti), received FDA approval. Shortly after, ixazomib (Ninlaro), the fourth drug for MM and first oral PI, was approved.

Oral Agents

Panobinostat

Panobinostat is an oral, nonselective histone deacetylase inhibitor that has anti-myeloma activity by modulating gene expression and inhibiting pathways involved in protein metabolism. It is approved for use in combination with bortezomib and dexamethasone in patients with R/R MM who have received at least two regimens containing an IMiD and bortezomib. The FDA approval was based on the phase III PANORAMA-1 that compared panobinostat or placebo in combination with bortezomib and dexamethasone. The study showed an improved median PFS in the panobinostat group (11.99 months vs. 8.08 months; p<0.0001), as well as a significantly higher rate of CR or near-CR (27.6% vs. 15.7%; p=0.00006). Common grade 3 or 4 adverse events associated with panobinostat include thrombocytopenia, lymphopenia,

diarrhea, asthenia, fatigue, nausea, and PN. The recommended starting dosage of panobinostat is 20 mg orally once every other day (i.e., three doses per week) on days 1, 3, 5, 8, 10, and 12 of a 21-day cycle for up to eight cycles. The medication may be continued for an additional eight cycles in patients who have clinical benefit and do not have medically significant or unresolved severe toxicity (Richardson 2016a; Richardson 2016b). Dosage modification may be required if toxicity occurs or in patients with hepatic impairment and when coadministered with strong CYP3A inhibitors because panobinostat is metabolized by the CYP3A enzyme. Panobinostat has a boxed warning to alert both patients and providers to the potential for severe diarrhea and cardiac toxicities during treatment.

Ixazomib

Ixazomib, the first oral PI approved by the FDA, is used in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy. The approval was based on the randomized, double-blind, placebo-controlled, multinational, phase III TOURMALINE-MM1 clinical trial, in which patients (median age 66 years) with R/R MM who had received one to three prior lines of therapy were randomized to an ixazomib group (n=360) or a placebo group (n=362), with all patients also receiving lenalidomide and dexamethasone. The median PFS in the ixazomib group was 20.6 months compared with 14.7 months in the placebo group (p=0.012). The ORR was 78.3% in the ixazomib group compared with 71.5% in the placebo group (p=0.035), with 11.7% versus 6.6% of patients having a CR (p=0.019) and 48.1% versus 39.0% of patients having a VGPR or better (p=0.014).

The most commonly reported adverse events among the ixazomib group versus placebo were diarrhea (45% vs. 39%), rash (36% vs. 23%), thrombocytopenia (19% vs. 9% grades 3/4), and PN (27% vs. 22%; mainly grades 1/2 and 2% grade 3 in each arm). The clinical trials with ixazomib had a low incidence of PN compared with similar studies evaluating bortezomib-related neuropathy, which may be attributed to the high specificity of ixazomib inhibiting the chymotrypsin-like site of the 20S proteasome. The recommended dosage regimen for ixazomib/lenalidomide/dexamethasone is ixazomib 4 mg on days 1, 8, and 15; lenalidomide 25 mg on days 1–21; and dexamethasone 40 mg on days 1, 8, 15, and 22 of a 28-day treatment cycle, with treatment continuing until disease progression or unacceptable toxicity. Dosage modification may be required if toxicity occurs, or in patients with hepatic or renal impairment. Because of the convenience of oral administration, ixazomib is a promising option for MM treatment and is being evaluated as a single agent and in combination with other therapies in phase III trials for patients with R/R MM and those with newly diagnosed disease and as a maintenance therapy (Moreau 2016; Kumar 2015).

Biologics

Daratumumab

Daratumumab is a fully humanized IgG1κ monoclonal antibody directed against CD38 that received FDA accelerated approval in November 2015 for the treatment of patients with MM who have received at least three prior lines of therapy, including a PI and an IMiD, or who are double refractory to a PI and an IMiD. The approval was based on the SIRIUS trial, an open-label, international, multicenter phase II study in which 106 patients with R/R MM who had received at least three prior lines of therapy including a PI and IMiD, or who were double refractory to a PI and IMiD, received daratumumab 16 mg/kg (n=106) until unacceptable toxicity or disease progression occurred. These patients had received a median of five prior lines of therapy before study entry. Daratumumab was given as 16 mg/kg intravenously per week for 8 weeks (cycles 1 and 2), followed by every 2 weeks for 16 weeks (cycles 3–6), and then every 4 weeks thereafter (cycle 7 and higher). Overall responses were noted in 31 patients (29.2%): 3 (2.8%) having a stringent CR, 10 (9.4%) having a very good PR, and 18 (17.0%) having a PR. The median duration of response was 7.4 months, and PFS was 3.7 months. The 12-month OS was 64.8%. Daratumumab was well tolerated, with the most common adverse reactions being infusion-related reactions (46% incidence of any grade infusion reaction with first dose), fatigue, nausea, back pain, fever, cough, thrombocytopenia, neutropenia, and anemia. Daratumumab is currently being studied in combination with other MM-approved drugs (e.g., lenalidomide, pomalidomide) with promising results. Daratumumab will cost around $6105 per infusion, which start out weekly and then change to biweekly, then monthly; at 23 doses, the first 6 months would cost $100,000, assuming the patient receives a dose of 16 mg/kg per the dosing schedule (no doses withheld) with a weight of 70 kg (Lonial 2016a; Lonial 2016b).

Recently, daratumumab received approval in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The first one was a phase 3 trial, on 569 patients with R/R MM who had received one or more previous lines of therapy to receive lenalidomide and dexamethasone alone or in combination with daratumumab. At a median follow-up of 13.5 months 169 events of disease progression or death were observed (18.5% in the daratumumab group vs. 41.0% in the control group; 95% CI, 0.27 to 0.52; p<0.001). A significantly higher rate of overall response was observed in the daratumumab group than in the control group (92.9% vs. 76.4%, p<0.001). The most common adverse events of grade 3 or 4 reported in the daratumumab group and the control group were neutropenia (51.9% vs. 37.0%), thrombocytopenia (12.7% vs. 13.5%), and anemia (12.4% vs. 19.6%). Daratumumab-associated infusion-related reactions occurred in 47.7% of the patients and were mostly of grade 1 or 2 (5.3%

grade 3) and they occurred during the first infusion (Dimopoulos 2016).

The second one was a phase 3 trial, on 498 patients with R/R MM who had received one or more previous lines of therapy to receive bortezomib and dexamethasone alone or in combination with daratumumab. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group and was 7.2 months in the control group (95% CI, 0.28 to 0.53; p<0.001). The rate of overall response was higher in the daratumumab group than in the control group (82.9% vs. 63.2%, p<0.001). The most common grade 3/4 adverse events reported in the daratumumab group and the control group were thrombocytopenia (45.3% vs 32.9%), anemia (14.4% vs 16.0%), and neutropenia (12.8% vs 4.2%). Infusion-related reactions were reported in 45.3% of the patients in the daratumumab group; these reactions were mostly grade 1 or 2 (grade 3 in 8.6%) and they occurred during the first infusion (Palumbo 2016).

Elotuzumab

Elotuzumab is a SLAMF7-directed immunostimulatory antibody that was FDA approved on November 30, 2015, to be used in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies. The randomized clinical trial that led to the approval of elotuzumab was ELOQUENT-2, a phase III open-label, randomized trial that included 646 patients with R/R MM who had received one to three previous regimens and had documented disease progression after their most recent therapy. Patients were randomized to receive elotuzumab/lenalidomide/dexamethasone or lenalidomide/dexamethasone. At 1 year, the PFS rate in the elotuzumab group was 68% versus 57% in the control group, and at 2 years, 41% versus 27%, respectively. Median PFS in the elotuzumab group was 19.4 months versus 14.9 months (p<0.001). The ORR was 79% in the elotuzumab group versus 66% in the control group (p<0.001). Common grade 3 or 4 adverse events in the two groups were lymphocytopenia (77% vs. 49%), neutropenia (34% vs. 44%), fatigue (8% vs. 8%), and pneumonia (15% vs. 11%). Infusion reactions occurred in 10% of patients in the elotuzumab group and were grade 1 or 2 in 29 patients. The recommended elotuzumab dose is 10 mg/kg given as an intravenous infusion every week for the first two cycles and every 2 weeks thereafter in conjunction with the recommended dosing of lenalidomide and low-dose dexamethasone. Elotuzumab will cost $5000 per infusion, which is given every week for the first two cycles then every 2 weeks thereafter; the first 6 months would cost $80,000, assuming the patient receives a dose of 10 mg/kg per the dosing schedule (no doses withheld) with a weight of 70 kg (Jakubowiak 2016).

SUPPORTIVE CARE

With the tremendous advances in therapy, patients with MM are living longer. Improving the quality of life for these patients through supportive care is equally as vital. Bone-related complications are present with disease presentation and progression. Patients with MM also face treatment-related challenges, including PN, thrombotic complications, and infections.

Bone Disease

Bone involvement is one of the defining characteristics of MM, either as lytic lesions or as osteopenia that is present at diagnosis. Bone involvement is often associated with pain and skeletal-related events (SREs) such as pathologic fracture, cord compression, and hypercalcemia, which may lead to surgery or radiation. Skeletal-related events increase mortality by 20%. Bisphosphonates such as pamidronate and zoledronic acid play a fundamental role in minimizing and managing bone-related complications and SREs. Intravenous pamidronate was one of the first bisphosphonates to show a significant reduction in SREs in MM. In patients with at least one osteolytic lesion, pamidronate (90 mg intravenously given every 4 weeks) significantly reduced SREs compared with placebo (24% vs. 41%, respectively; p<0.001) after nine cycles. Time to first pathologic fracture or first radiation treatment was longer in the pamidronate-treated group. In addition, pamidronate significantly improved quality of life, with decreases in pain scores within 1 month. Zoledronic acid, which is more potent than pamidronate, has comparable efficacy with pamidronate in MM with the advantage of a shorter infusion time.

In addition to playing an important supportive role, bisphosphonates may have an anti-MM effect. The MRC Myeloma IX trial compared zoledronic acid and oral clodronate in patients with newly diagnosed MM in addition to myeloma-directed therapy. This study found that zoledronic acid reduced mortality by 16% and increased median OS from 44.5 months to 50.0 months (p=0.04). In addition, at a median follow-up of 3.7 years, the incidence of SREs was lower with zoledronic acid (27% vs. 35%; p=0.0004).

One of the most serious complications of bisphosphonates is osteonecrosis of the jaw (ONJ). Osteonecrosis of the jaw is traditionally defined as exposed, necrotic bone of the jaw that does not heal after 8 weeks and is generally painful. Zoledronic acid is associated with the highest risk of ONJ, which is attributed to its increased potency. Earlier studies suggested an incidence of 4%–11% that correlates to exposure duration. Treatment of ONJ is supportive; patients are advised to maintain good dental hygiene and to minimize invasive procedures (e.g., tooth extractions, dental implants) during bisphosphonate therapy. The IMWG guidelines recommend suspending bisphosphonate therapy for 90 days before and after invasive dental procedures. Routine dental cleanings and procedures, including root canals, may proceed as usual.

Nephrotoxicity may occur with intravenous bisphosphonates. Monitoring renal function is essential, and adjusting

the dose is recommended, depending on the extent of the renal toxicity present.

The IMWG guidelines recommend that bisphosphonates be given until disease progression in patients not having a CR or VGPR. With the increased risk of adverse events with prolonged use, the IMWG panel recommends monthly administration for at least 12–24 months of treatment for patients achieving CR or VGPR (timing from start of treatment), and thereafter, at the discretion of the provider. Mayo Clinic consensus statement recommends reducing frequency of administration to every 3 months dosing after the 2 year period instead of discontinuing it. In patients who experience relapse, bisphosphonates should be reinstituted (Lacy 2006).

Common adverse effects with bisphosphonates are often infusion related and can occur 24–48 hours post-infusion; they include flu-like symptoms, fatigue, nausea, and electrolyte abnormalities. It is recommended that all patients receiving these agents also receive a 500-mg calcium supplement and 400 international units of vitamin D per day.

Denosumab, an osteoclast inhibitor, may play a role in the supportive care of MM-associated bone disease, but it is not currently FDA approved for use in patients with MM. Denosumab is a monoclonal antibody, given subcutaneously, that inhibits osteoclast activity by targeting RANKL (receptor activator of nuclear factor κ-B ligand). Denosumab is approved for increasing bone density in patients with osteoporosis and for preventing SREs in patients with metastatic bone disease from solid tumors. A phase III study of MM showed inferior survival, even though denosumab was comparable with zoledronic acid with respect to SREs. A larger, ongoing phase III study will compare denosumab with zoledronic acid in patients with MM (NCCN 2016; Hameed 2014).

Thromboembolism

Patients with MM have an increased risk of venous thromboembolism (VTE). Although thrombotic events are predominantly venous, arterial events have occasionally occurred. The highest risk of VTE is in the first year after diagnosis and is significantly increased with IMiDs such as thalidomide, lenalidomide, and pomalidomide.

As single agents, thalidomide and lenalidomide have a VTE risk of less than 5%. The risk of VTE increases with the addition of other medications such as high-dose dexamethasone, anthracyclines, or erythropoietin; or other factors, including age 65 and older, obesity, cardiac history, previous VTE, surgery, comorbid conditions (diabetes, infections, cardiac diseases), and inherited thrombophilia.

The IMWG guidelines recommend risk stratification. Patients with MM receiving IMiDs with one or no VTE risk factors should receive aspirin 81–325 mg daily. For patients with MM with more than one risk factor receiving IMiDs, prophylactic doses of low-molecular-weight heparin or therapeutic warfarin with a goal INR of 2–3 are recommended (Palumbo 2008).

Peripheral Neuropathy

Peripheral neuropathy is one of the principal dose-limiting adverse effects of MM therapy and is associated with significant effects on the patient's quality of life. Peripheral neuropathy is most significant in patients who receive thalidomide and bortezomib. Symptoms of PN include a burning sensation, paresthesia, discomfort, and neuropathic pain or weakness, which may start distally with the toes and fingers and progress proximally.

Bortezomib-induced PN is reversible, but neuropathy can cause significant dose reduction and treatment discontinuation. In the SUMMIT and CREST phase II trials of bortezomib for relapsed MM, PN occurred in 35% of patients, including 13% who had grade 3 or higher PN. Dose reductions occurred in 12% of patients, and 5% of patients discontinued therapy because of PN. These patients were receiving the twice-weekly dose of intravenous bortezomib on a 21-day cycle. Because of the frequency of PN in initial studies of bortezomib, a dose-modification schedule was adopted in the phase III APEX trial of bortezomib (Table 2-10). This resulted in a reduction in the frequency of grade 3 or higher PN to 9%.

To improve the tolerability of treatment, bortezomib can be been given weekly rather than twice weekly or given subcutaneously rather than intravenously. In a phase III trial, bortezomib intravenously was initially given twice weekly for the first four cycles and then weekly in subsequent cycles. Efficacy was similar between the groups with respect to PFS, CR rate, and 3-year OS rate when comparing bortezomib given weekly or twice weekly. The patients receiving twice-weekly bortezomib had a significantly higher incidence of grade 3 or greater PN (28% vs. 8%; $p<0.001$), together with a higher discontinuation rate because of neuropathy (15% vs. 5%; $p<0.001$).

Changing the route of administration of bortezomib from intravenous to subcutaneous was investigated in a randomized study of patients with relapsed disease (see earlier section on the treatment of R/R MM). Given the remarkably improved tolerability, subcutaneous bortezomib is now FDA approved and commonly used in the relapsed and newly diagnosed settings.

Table 2-10. BOR Dose Modification for Peripheral Neuropathy

Peripheral Neuropathy	Dose Modification
Grade 1 without pain	Continue same dose
Grade 1 with pain	Reduce to 1 mg/m^2
Grade 2 with pain or grade 3	Hold treatment and reinitiate at 0.7 mg/m^2 once weekly when resolved
Grade 4	Discontinue

In contrast to bortezomib, carfilzomib and ixazomib are new PIs that are associated with a low incidence of PN. Adding ixazomib to a regimen of lenalidomide and dexamethasone resulted in 27% of patients having PN versus 22% in the placebo arm. Only 2% of patients in the ixazomib arm had grade 3 PN compared with 6% of patients who received subcutaneous bortezomib and 3% of patients who received carfilzomib in other studies.

There is no known effective treatment of PN. Recognizing the early signs of PN is critical so that dose modifications can be made to increase the chances of reversibility. Once present, treatment is supportive and based on consensus guidelines and extrapolation of treatments used in other settings, such as diabetic PN or postherpetic neuralgia. Conventional treatments for neuropathy include opioids, gabapentin, pregabalin, tricyclic antidepressants, duloxetine, topical agents such as capsaicin cream or menthol, and emollients such as cocoa butter. However, results have been inconsistent, and treatment is based on patient and physician preference.

Although the findings regarding their use are conflicting, supplements such as vitamin E, glutamine, α-lipoic acid, and omega-3 fish oil have also been used. Vitamin C is not recommended because in vitro vitamin C inactivates bortezomib (Richardson 2012).

Prevention of Infection

Infections are a major cause of morbidity and mortality in patients with MM and can be attributed to the effects of MM on humoral and cellular immunity as well as myelosuppression from treatment. Patients with MM have functional hypogammaglobulinemia and may require immunoglobulin replacement (intravenous immunoglobulin [IVIG]). Findings of IVIG from various studies have been inconsistent, but IVIG may be considered in selected patients with severe, recurrent infections and hypogammaglobulinemia.

Bortezomib is associated with a significantly higher risk of herpes zoster. In the phase III APEX trial, the incidence of herpes zoster was 13% among patients treated with bortezomib compared with 5% in the control arm receiving dexamethasone alone (p=0.0002). In clinical practice, antiviral agents such as acyclovir (e.g., 400 mg orally twice daily) are recommended as prophylaxis because of the high risk of herpes zoster associated with bortezomib. Antiviral therapy is also indicated with the newer PIs carfilzomib and ixazomib (Rollig 2015; Vesole 2012; Oken 1996). Trimethoprim/sulfamethoxazole is also indicated for patients taking long-term corticosteroid-containing regimens to prevent *Pneumocystis jiroveci* pneumonia.

CONCLUSION

Diagnosis and treatment of MM has changed dramatically in the past decade. Advances in therapy have resulted in a marked improvement in OS. New drugs introduced in the past few years include carfilzomib, pomalidomide, panobinostat, ixazomib, elotuzumab, and daratumumab. The growing knowledge about pathogenic mechanisms, development of novel effective compounds that target both MM cells and the microenvironment, and development of more effective supportive strategies have led to a prolonged median OS in patients with MM.

Practice Points

MM accounts for 10% of hematologic cancers and is incurable. For transplant-eligible patients, induction therapy followed by ASCT is most appropriate. The best therapy is an induction regimen and transplantation for eligible patients. Maintenance therapy has been shown to prevent PFS and therefore is included in the guidelines as a treatment of MM. Many patients progress after first-line therapy, including ASCT, and need additional treatment to control their disease.

- **NCCN lists several agents/regimens as preferred first line as well as alternatives for relapsed MM. All the agents have a role in MM as preferred first-line agents and alternatives as well as treatment for relapsed disease.**
- **Proteasome-based therapy alone or in combination with IMiDs and dexamethasone is the backbone of MM therapy.**
- **For patients whose disease has relapsed, there are many treatment options. Yet head-to-head studies are very rare. Factors to consider when choosing therapy for relapsed disease are previous treatment response, ease of administration, and adverse effect profile.**
- **Newer agents have been approved in recent years, including panobinostat, ixazomib, daratumumab, and elotuzumab. All of these agents are approved in the R/R setting.**
- **Panobinostat is approved in combination with bortezomib and dexamethasone. The most common adverse effects with this regimen are fatigue, nausea, and diarrhea. In addition, there is a boxed warning regarding cardiac toxicities; therefore, patients with a cardiac history should be very closely monitored.**
- **Ixazomib is approved in combination with lenalidomide and dexamethasone, and the most common adverse effects with this regimen are diarrhea, rash, and thrombocytopenia. Peripheral neuropathy is very low compared with bortezomib.**
- **Daratumumab is approved as a single agent; however, studies are looking for combinations with a PI and IMiDs. One of the most common adverse effects with this drug is infusion reaction, which is more likely to occur during the first two infusions.**
- **Elotuzumab is approved in combination with lenalidomide and dexamethasone. The most common adverse effects with this regimen were infusion reactions.**
- **Pharmacists play a role in counseling patients on the adverse effects of these myeloma drugs in addition to the importance of adhering to the oral agents.**
- **Another large role for pharmacists is in providing supportive care for patients with MM. These include use of bisphosphonates for bone disease, prevention of infection – especially prophylaxis of zoster – with the use of PIs, and VTE prevention with the use of IMiDs.**

Our role as pharmacists is to counsel patients on the adverse effects of these myeloma drugs in addition to the importance of adhering to the oral agents. Providing supportive care is also a large part of the pharmacist's role. Bortezomib can cause neuropathy; thus, recognizing that adverse effect early on can help prevent worsening of the PN. Immunomodulatory drugs can cause VTEs; thus, patients must be anticoagulated properly, according to approved guidelines. Newer monoclonals have a high risk of infusion reaction; therefore, patients should be premedicated appropriately.

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Self-Assessment Questions

21. A 57-year-old African American man has newly diagnosed multiple myeloma (MM). His cytogenetics show he has t(4;14), and he states that his second cousin had acute myeloid leukemia. Which one of the following factors placed this patient at greatest risk of developing MM?

    A. Race
    B. Cytogenetics
    C. Age
    D. Family history

22. A 64-year-old man presents to the clinic with newly diagnosed MM. Which one of the following complications is most likely to develop in this patient if his MM is left untreated?

    A. Acute renal failure
    B. Cardiomyopathy
    C. Diarrhea
    D. Liver failure

23. A 62-year-old man presents to the clinic for evaluation of back pain. His calcium is 13 g/dL, and the only other information available for the patient is that his bone marrow (BM) biopsy reveals 15% plasma cells. Other laboratory tests and scan results have not yet returned. Which one of the following diagnoses is the most likely cause of this patient's presenting symptoms?

    A. Monoclonal gammopathy of undetermined significance (MGUS)
    B. Smoldering multiple myeloma (SMM)
    C. MM
    D. Non-Hodgkin lymphoma

24. Which one of the following patients is most likely to have SMM?

    A. BM biopsy with greater than 10% plasma cells in the BM, no monoclonal protein in blood, and presence of lytic bone lesions
    B. BM biopsy with greater than 10% plasma cells in the BM, abnormal serum free light chain ratio, and hypercalcemia
    C. BM biopsy with less than 10% plasma cells in the BM, monoclonal protein in blood, and osteoporosis
    D. BM biopsy with greater than 10% plasma cells in the BM, monoclonal protein of 3 g/dL or greater in blood, and no end-organ damage

25. A patient with MGUS is concerned about her disease and has many questions. Which one of the following statements is most accurate regarding MGUS?

    A. About 1% of cases progress to MM each year.
    B. It is thought to be the precursor of about 50% of cases of MM.
    C. It is associated with clinical symptoms.
    D. It is defined as greater than 20% plasma cells in the BM.

26. A patient with MM has Hgb 8 g/dL, β_2 microglobulin (B2M) 6 g/dL, calcium 11 mg/dL, M-protein 2 g/dL, and albumin 3 g/dL. When using the R-ISS, which one of the following criteria is most important to consider for this patient?

    A. Hemoglobin and B2M
    B. B2M and albumin
    C. B2M and calcium
    D. Albumin and M-protein

27. A patient with myeloma undergoes several tests, which show B2M 2.5 mg/L, t(4;14), deletion 13, and LDH 200 U/L. Which one of the following results would most accurately be considered a poor prognostic feature in this patient with newly diagnosed myeloma?

    A. t(4;14)
    B. B2M of 2.5 mg/L
    C. LDH of 200 U/L
    D. Deletion 13

28. A 64-year-old man receives a diagnosis of MM; he has no other comorbidities. Which one of the following is best to recommend for this patient?

    A. Four courses of induction chemotherapy, followed by conditioning and autologous stem cell transplantation (ASCT)
    B. Monthly courses of oral melphalan with prednisolone until the monoclonal protein concentration reaches a plateau; then thalidomide maintenance
    C. High-dose chemotherapy followed by a related donor allogeneic SCT
    D. Elotuzumab in combination with lenalidomide and dexamethasone

29. A 60-year-old transplant-eligible patient with newly diagnosed MM is starting therapy and asks what her options are. Which one of the following regimens is best to recommend for this patient?

    A. Bendamustine
    B. Bortezomib/lenalidomide/dexamethasone
    C. Melphalan/prednisone
    D. Carfilzomib/dexamethasone

30. In which one of the following patients would it be most urgent to start treatment?

    A. Incidental finding of a high M-spike during laboratory tests
    B. IgG 2 g/dL and BM biopsy revealing 20% plasma cells with no other symptoms

C. IgG 4 g/dL, BM biopsy of 10% plasma cells, and Hgb of 8 g/dL and fatigue
D. IgG 4 g/dL and BM biopsy of 30% plasma cells but no other symptoms

31. A patient with myeloma has had a posttransplant relapse. Which one of the following is the best option to recommend next for this patient?

A. Give bortezomib-based therapy.
B. Give lenalidomide-based therapy.
C. Give conventional chemotherapy such as dexamethasone/cyclophosphamide/etoposide/cisplatin.
D. Base the decision on what the patient received previously and the patient's comorbidities.

32. A MM patient's therapy is being changed from bortezomib to carfilzomib. The patient wishes to know the difference between these agents. Which one of the following responses best answers this patient's question about carfilzomib?

A. It is given once a month IV at dose of 27 mg/m^2.
B. It can be given subcutaneously.
C. It is only approved in combination with daratumumab.
D. It causes less neuropathy than bortezomib.

33. A patient is initiated on lenalidomide after having severe neuropathy with thalidomide. The patient wishes to know the difference between these agents. Which one of the following responses best answers this patient's question?

A. Lenalidomide is more potent than thalidomide.
B. Lenalidomide causes more neuropathy than thalidomide.
C. Anticoagulation is only needed with thalidomide.
D. The rate of myelosuppression is higher with thalidomide.

34. A 65-year-old man was given a diagnosis of MM in April 2011 and initiated on lenalidomide/bortezomib/dexamethasone. He underwent transplantation in May 2012. In July 2015, he relapsed and was initiated on lenalidomide/dexamethasone. After taking lenalidomide/dexamethasone for 5 months, the patient is refractory to that treatment and must start new therapy for relapsed/refractory (R/R) MM. He has renal disease with a CrCl of 35 mL/minute/1.73 m^2. The patient also has congestive heart failure. Which one of the following is best to recommend for this patient?

A. Daratumumab/bortezomib/dexamethasone
B. Lenalidomide/dexamethasone
C. Panobinostat/bortezomib/dexamethasone
D. Carfilzomib and dexamethasone

35. A patient with SMM has been reading blogs about myeloma, learning that patients with SMM can receive daratumumab, too. Which one of the following counseling points is best to give this patient regarding daratumumab?

A. Patients need not be on antiviral prophylaxis unless they receive it with bortezomib.
B. It is approved for patients with MM who have received three or more lines of prior therapy, including a PI and an immunomodulatory drug.
C. It is FDA approved for use in combination with lenalidomide.
D. Patients do not need premedication because it is a human monoclonal antibody.

36. A patient with a new diagnosis of myeloma is in the clinic for counseling on the use of bortezomib before starting her first cycle. Which one of the following counseling points is best to discuss with this patient?

A. Antiviral prophylaxis is only recommended in patients with a history of herpes zoster.
B. Peripheral neuropathy (PN) is one of the adverse effects.
C. Bortezomib needs a dose reduction with a CrCl less than 50 mL/minute/1.73 m^2.
D. PN is reversible; thus, there is no need for a dose reduction, if she has it.

37. While staffing in the pharmacy, you receive an order for zoledronic acid 4 mg intravenously for a patient with MM. Which one of the following options is best to monitor in a patient receiving bisphosphonates?

A. Renal function and LDH
B. Calcium and 25-hydroxyvitamin D
C. Osteonecrosis of the jaw (ONJ) and renal function
D. Calcium and thyroid-stimulating hormone (TSH)

38. A patient with MM starts treatment with bortezomib (1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of a 21-day cycle)/lenalidomide (25 mg/day orally 2 weeks on 1 week off), and dexamethasone (20 mg/day orally on days of bortezomib) regimen. After three cycles, the patient has complaints of tingling in the toes and some pain (grade 3 neuropathy). Which one of the following is best to recommend for this patient?

A. Start gabapentin immediately at a dose of 300 mg starting at night; increase to 300 mg twice daily; then three times daily.
B. Hold bortezomib and assess neuropathy in a week.
C. Dose-reduce bortezomib to 1 mg/m^2 IV on days 1, 4, 8, and 11.
D. Refer the patient to the primary care physician because this is unrelated to the disease or treatment.

39. The primary care physician for a patient with MM wants to initiate denosumab. The patient has received bisphosphonates in the past but had many adverse effects, so the patient does not want to take bisphosphonates. Which one of the following statements is best to share with this patient's care team regarding denosumab use?

    A. Denosumab showed a decrease in skeletal-related events (SREs) in patients with myeloma in addition to an increase in progression-free survival in clinical trials.
    B. Before giving denosumab to this patient, baseline measurements of creatinine, serum calcium, magnesium, and phosphorous should be checked.
    C. Denosumab should not be given to this patient because of his intolerance of the bisphosphonate, which translates to intolerance of denosumab.
    D. Denosumab should not be given to this patient because studies have shown negative results on survival in the myeloma population.

40. A 70-year-old woman (BMI 31 kg/m^2) is given a diagnosis of MM and will be starting lenalidomide therapy. She has no cardiac or venous thromboembolism (VTE) history. Which one of the following is best to recommend for this patient?

    A. Aspirin 325 mg orally daily
    B. Warfarin with target INR of 2–3
    C. Rivaroxaban 20 mg orally daily
    D. No need for anticoagulation

Learner Chapter Evaluation: Multiple Myeloma.

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

19. The content of the chapter met my educational needs.
20. The content of the chapter satisfied my expectations.
21. The author presented the chapter content effectively.
22. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
23. The content of the chapter was objective and balanced.
24. The content of the chapter is free of bias, promotion, and advertisement of commercial products.
25. The content of the chapter was useful to me.
26. The teaching and learning methods used in the chapter were effective.
27. The active learning methods used in the chapter were effective.
28. The learning assessment activities used in the chapter were effective.
29. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

30. Demonstrate knowledge of the pathogenesis and risk factors for multiple myeloma (MM) as well as the clinical presentation of the disease.
31. Distinguish the different staging systems and the response criteria used in MM.
32. Evaluate patients with myeloma and design the appropriate treatment options, including new therapies.
33. Justify supportive care for issues including bone disease, thromboembolism, neuropathy, and prevention of infection associated with myeloma disease and treatment.

Questions 34–36 apply to the entire learning module.

34. How long did it take you to read the instructional materials in this module?
35. How long did it take you to read and answer the assessment questions in this module?
36. Please provide any additional comments you may have regarding this module:

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